MATERNAL MALNUTRITION AND CONGENITAL DEFORMITY[1]

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In the United States of America in the year 1955-56, 350,000 mothers delivered premature babies; 285,000 babies were born with congenital malformation; and fatal disease and defects took 165,000 infant lives in the perinatal period. Deaths associated with birth were exceeded only by heart, cancer and cerebral hemorrhage deaths. Fetal deaths among non-whites were almost double that obtaining among the whites, and perinatal (foetal and neonatal) losses occurred in a ratio of about 2:3 in whites and non-whites. In all likelihood, prematurity is only incidental to malformation which interferes with proper nutrition and growth. There are as of now 500,000 people with cerebral palsy, 300,000 with epilepsy, and 1,500,000 are mentally retarded. About 1 per cent of reported births are infants with lethal or handicapping malformations diagnosed at or some time after birth. Congenital malformations account now for about 14 per cent of all infant deaths in the U. S., and 20 per cent in New Zealand where infant death rates are lower than in the U. S.

For the first quarter of 1950, the National Office of Vital Statistics reported a neonatal mortality from malformations of 4.4 per 1,000 births, with twice the frequency in whites (4.7) as in non-whites (2.7). For infants weighing over 2,500 g (5 pounds), malformation was blamed for 24 per cent of the deaths, and for infants weighing 2,500 g or less, malformations ranked fourth and accounted for only 7 per cent of deaths.

Hertig and Rock (1949) reported abnormalities in 36 per cent of early human conceptuses they removed from the uterus. Streeter estimated the incidence of defective embryos in Vertebrates to be about 12 per cent. Since about 20 per cent of all pregnancies terminate before the period of reportability at 20 weeks, the frequency of abnormal development must be many times the figures given for reported fetal and neonatal deaths.

The life of man as a new entity or individual, begins not at birth, but some 280 days (10 lunar months) previously at the time of ovulation, fertilization and cleavage. Sir Thomas Browne knew this well when he wrote in 1642 in his "Religio Medici" as follows: "And surely we are all out of computation of our age, and every man is some months elder than he bethinks him; for we live, move, have being, and are subject to the action of the elements and the malice of diseases, in that other world, the truest microcosm, the womb of our mother."

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(1) An address delivered March 17, 1958 to the Grants Pass, Oregon, chapter of N.F.A. A bibliography of eighty (80) references to the literature on congenital deformity, is available upon request.

It is during prenatal life, an area hitherto neglected or at best given perfunctory attention, that misfortunes occur earlier or later. These accidents are occasioned by either hereditary or environmental factors or by a combination thereof, leading if not to death, then to varying degrees of clinical and subclinical structural deviations and/or functions. These in turn may, depending on circumstances and severity, threaten health and/or compromise longevity.

Primitively and historically, people would consider the congenitally deformed infant as a divine visitation and a good omen, or as a curse and so destroy it, or as an undesirable arrival compromising the physical prowess of the nation and so also destroy it. Fanciful creatures like the one-eyed Cyclops, Fauns with pointed ears, the two-headed or faced Roman god Janus had a basis in fact. Even the mother which bore a monster may have been tried on metaphysical grounds and burned to death.

But with the advent of rational approaches to the problems of man, there developed an understanding of the physico-chemical mechanisms involved in the induction of developmental and functional abnormalities and anomalies. Thus there has evolved a distinct discipline designated as Prenatal Pediatrics, or Prenatal Public Health -- a subject which concerns the welfare of that portion of the human population in the womb of woman.

Some of the earliest scientific investigations in teratology (study of monsters) were carried out by the French biologist, Isidore Geoffroy Saint-Hilaire in his three-volume work of 1832 entitled "The General and Particular History of Anomalies of Organization in Man and Animals," and by the French Camille Dareste about a half century later. Saint-Hilaire concluded that congenital deformities were "the effects of disturbances and adverse influences happening during the course of development" and emphasized that pregnancy misadventures were vital subjects for research, and as he says, "a subject important, immense and capital". The 18th century English biologist and surgeon John Hunter (1728-93) was interested in monstrosities. J. W. Ballantyne of Edinburgh made some notable efforts in the solution of some problems of malformation in his classical books of 1895 and 1904, viz., "The Diseases and Deformities of the Foetus", and, "The Manual of Antenatal Pathology and Hygiene".

Early mechanistic explanations for congenital malformation included the following hypotheses: (1) Mechanical and hydrostatic or hydraulic pressure theory, (2) Bleb theory, (3) Foetal dysplasia theory, (4) Circulatory failure theory, (5) Muscular derangement, (6) Atavistic theory, (7) Archipterygial theory, (8) Organiser theory, and the (9) Genetic theory.

In recent times, congenital defects have all too often been explained on a genetic basis, meaning that defective genes (the factors of heredity) cause corresponding defects in development, organization and function. We know

very well that inheritance IS responsible for some deformities, some inborn errors of metabolism, and for some susceptibilities to imperfect development and to diseases. (Genes are also invariably involved in the incident about the professor teaching at a small state college of agriculture when a proposal was brought before the legislature for salary raises. The farm bloc was solidly against the measure and couldn't see why the state should pay college professors $5,000 per year just for talking 12-15 hours per week. Faculty representations made no headway with this bloc until this professor who had some farming experience, suddenly got an inspiration. "Gentlemen," he told the law makers, "a college professor is a little like a bull. It's not so much the amount of time he spends, as it is the importance of what he does." -- The professors got their raise.)

Prior to the discovery of pellagra (a vitamin deficiency disease), the importance of genetic determinants in its etiology received what now is considered undue emphasis. We also know that an embryo which began its life with a perfectly normal set of genes, may suffer from crippling deformities arising from injuries delivered to the embryo at certain stages of its development. It is generally acknowledged that the vast majority of defects arise not from defective gene operation, but from divers and sundry environmental factors. One hastens to add that some defects, structural and/or functional, are occasioned by a combination of a genetic predisposition and environmental factors. The type of lethal factor (recognized in over 80 conditions in birds, rodents, cattle and other animals) in which a gene when heterozygous produces only a mild variation from the normal pattern, but when homozygous produces a malformation incompatible with survival, has never been proven to exist in man except for sickle-cell anemia (Allison) in the negro and a few other possible exceptions (Mediterranean anemia - Ceppellini). The part played by heredity is made difficult to assess because so many different noxious agents have been experimentally demonstrated to produce malformations identical to those which may be induced by gene defect. Thus genetic disturbances can rarely be shown to be the cause of lethal malformations.

This revised view with increased deference to environmental factors was given impetus by the epidemic outbreak of German measles in 1941 which left a year later in the wake of this mild disease, a train of blind, deaf, heart-diseased, and mentally retarded infants among babies born of pregnant women who had the infection. No longer could man dismiss fatalistically and complacently, these aberrations as either acts of God or genetic accidents.

It was soon learned also that maternal sensitivity to fetal Rh positive blood, could destroy, maim and otherwise compromise the unborn infant with erythroblastosis foetalis. Repetitive accumulation might even destroy the gravid mother. Exposure of premature babies to excessive oxygen pressure in incubators was found to cause blindness (retrolental fibroplasia), and atomic radiation at Hiroshima and Nagasaki caused mothers exposed thereto, to give birth to mongoloid babies (shortened skulls, defective brains).

Congenital defects, fatal and non-fatal, which may be of purely genetic origin, include among others, the following examples: certain types of hare-lip (dominant), cleft palate (dominant), club foot, digital abnormalities, achondroplasia (dominant), osteopsathyrosis, lower lip fistulae (dominant), benign brachydactyly, polydactyly, ectrodactyly (split-hand), acheiropodia, spina bifida, chondrodystrophy (has a stronger effect of paternal than maternal age), mongolism (effect of maternal age is greater than paternal if genetic at all); epiloia, neurofibromatosis, and retinoblastoma (dominant), all three of which show very slight effects of paternal age; phenylpyruvic oligophrenia, and certain inborn errors of metabolism such as, defects in bilirubin glucuronide synthesis, congenital galactosemia, and congenital agammaglobulinemia.

In addition to those defects which may be purely genetic in man, there are numerous defects which arise from many different types of environmental factors. Here we should include the lethal and abnormal conditions of the embryo which may result from maternal infections concurrent with pregnancy --viruses which may affect the fetus, such as mumps, influenza A, chicken pox, herpes zoster, polio-myelitis, Newcastle and Rubella or measles. The sporozoon of toxoplasmosis must also be reckoned, and so also the plasmodial agent of congenital malaria, the Treponema pallida of congenital syphilis, as well as certain parasitic affections involving the helminths.

Another group of teratogenic factors include low oxygen levels (intrauterine hypoxia, anoxia which may lead to non-genetic mongolism), high oxygen levels (oxygen toxicity which may lead to retrolental fibroplasia), low atmospheric pressure, and high atmospheric pressure.

In another category of defect inducers we may include various chemicals such as azaserine; 8-azaguanine; the dyes trypan blue, azo blue and Evans blue; Lathyrus odoratus factor; sucrose; pilocarpine, pilocarpidine and their isomers; reserpine; eserine; thallium nitrate; lead nitrate (induces hydrocephalus, meningoencephalocoeles and meningo-myelocoeles); boric acid; lithium chloride; ethyl carbamate; benzimidazole and benzotriazole derivatives; 4-aminopteroglutamic acid; drugs and metallic poisons given during pregnancy; ricine; trypaflavine; saponine; soluseptasine; colchicine; 3-acetylpyridine; streptomycin (congenital deafness producer); and the radiomimetic substances such as nitrogen mustard. At this point we should add that 41.5 per cent of the deaf in the U. S. are considered as congenital cases. Alcohol passes the placental barrier and its effects must be assessed. (Speaking of alcohol brings to mind the late Robert Benchley who was drinking martinis mixed with second rate gin one day when a friend passed by and warned his friend anxiously: "Don't you know that stuff is slow poison?" "Oh, that's all right," said Benchley, "I'm in no hurry.") Smoking causes tachycardia in the fetus also, and stillbirths in animals have been increased tenfold when exposed to the equivalent of 20 cigarettes per day. There is increasing evidence that agents well tolerated by the mother can easily damage the unborn child. Some 15 or more chemical agents have been shown to have teratogenic

activity in just mammals. Certain agents although as different in nature as sulfanilamide and eserine, may act through the same mechanism and thus produce the same pattern of defects. Thus either x-rays or azo dyes or vitamin A deficiency can cause interventricular septal defects, and also a variety of great artery defects. That different agents produce different patterns of abnormality implies that they either act at different times in development or on different phases of the developmental process at any given time; hence x-rays administered on the 9th day (rat) cause ocular and cerebral abnormalities, but when given on the 14th day, cause skeletal defects. It appears equally clear that x-rays, and vitamin A deficiency exert effects on different mechanisms, or perhaps on different phases of metabolism of the embryo. Various agents may exhibit a specificity of teratogenic action. There is then, both time-specificity and agent-specificity.

Some hormones which may produce anomaly include insulin (exencephaly, umbilical hernia, rib fusion), and cortisone which in excess produces cleft palate, and in deficiency of the adrenal gland may lead to mongolism. Excess emotion with hormonal effects can be teratogenic. Maternal metabolic disorders, diabetes, hyper- and hypoglycemia may be teratogenic.

In a class by itself is iso-immunization wherein we consider Rh-incompatibility and infant deformity. Electroshock treatment during pregnancy can cause mental deficiency in the offspring. Congenital malformation can result from amniotic sac puncture. Direct physical trauma or mechanical injury to the fetal tissues takes its toll, and so also thermal injury, hyaline membrane formation, toxemia of pregnancy (may be caused by protein deficiency), maternal limitation (uterine), overripeness of eggs (may lead to twinning and monsters) and advanced maternal age (mongolism), as well as tubal and extra-uterine or abdominal gestation, diseases and disorders of the uterus, lesions of the placenta, placenta praevia, etc.

Reproduction immediately after puberty results in an increased possibility of anomalies. In women under 20 years of age, 7.8 per cent of mothers giving birth to malformed babies were in this age group. In mothers under 15 years of age, the malformation rate is 22.5 per 1,000 births; in mothers 15-19 years of age, the rate is 8.6 per 1,000 births; in mothers 20-25 years of age, the rate is lowest, namely 7.1 per 1,000 births.

How about older women? Women over 35 years of age gave birth to 12.72 per cent of all births, but of these older women 16.25 per cent belonged to the group of women giving birth to malformed children. In mothers 40-44 years old there is an incidence of 11.3 malformations per 1000 births, and in mothers over 44 years old, the incidence is 26. The incidence was lowest in the 25-29 age group, with 6.4 per 1,000.

The incidence of mongolism rises rapidly with increasing age after the 35th year; it occurs 40 times more often in mothers over 45 than in mothers 20-30

years old. Although mothers over 40 comprise only 2-4 per cent of all pregnant women, yet these gave birth to 1/3 of all mongoloid babies. There are now some 600,000 living mongoloids. Mongolism is related to maternal age and thought not to result from gene mutation.

Increased age in either parent, as well as an increased difference in age between father and mother, are implicated in the causation of achondroplasia. For epiloia, neurofibromatosis, or retinoblastoma, present at birth or shortly thereafter, there may be slight effects of paternal age. Thus the older germ cells possessed by older parents might likely undergo deterioration in the form of genetic changes, involving failure of the gene duplication process at the time of cell division, irradiation from natural sources, and action of chemical mutagenic agents during the lifetime of the parents. Thus three causes would be expected to be cumulative in action, i.e., should show an "age effect". Thus mutational genetic phenomena may very well be age-correlated, and this may be the case also with neurofibromatosis.

The malformation rate is higher in male than in female babies, the ratio being 123.8 males to 100 females. Of 40 fetuses and infants with complete renal agenesis at necropsy (Chicago), 36 were male, 4 female. Exceptional however is the fact that of 49 babies delivered with anencephalus, 40 were female, 4 male.

The phenomenon of multiple births increases the incidence of malformation, which is 9.2 per 1,000 live births in twins contrasted with the overall rate of 7.2. The rate of twinning rises progressively to age 40. The presence of twins and the likelihood of malformations increase progressively with the advance in years.

A further group of defect-producing agents includes the several forms of radiation: x-ray; radium; ultraviolet radiation; cosmic radiation; atom bomb fall out; Strontium 90 (replaces calcium in bone); atom bomb blasts (leukemia, microcephaly, mental retardation, mongolism); radio-phosphorus; Barium 140, Cesium 137, and Lanthanum 140.

There remains one other set of factors which may be operable in the production of functional and structural deformity, which are best arranged under the heading of maternal nutritional deficiency and hyper-states. Related in this consideration are the vitamin antagonists and analogs.

It is this general area of the maternal nutritional status and its relation to defect in the offspring which is selected for special development here and now, with emphasis on specific deficiencies of metabolites, specific excesses, as well as the interaction among them. Certain vitamins play a highly significant role in embryonic differentiation and organogenesis.

Accordingly we may as well begin our discussion alphabetically with vitamin A! And for want of space and time, we summarize the findings of research and clinical experience.

VITAMIN A. Maternal vitamin A deficiency in various degrees can cause the following untoward effects: infertility of the egg; premature degeneration of the egg; marked reduction in number of adult animals mating; marked reduction in conception as compared with controls among those which do mate; progressive loss of conceptus due to resorption earlier and abortion later in pregnancy and birth of dead young; mottled placenta with decreased vascularity; defects of the fetal eyes, diaphragm, kidneys, ureters, genital ducts, heart, lungs, aortic arches, and lower genito-urinary tract, congenital hydrocephalus; sterility of the female due to diminished uterine glycogen, stratified squamous metaplasia of glandular uterine epithelium and general epithelial changes in the female reproductive tract; and degenerative changes in the seminiferous tubules of the testis, a reversible change.

Vitamin A in excess in nursing infants will induce acute hydrocephaly with vomiting, and in embryos will cause cranial deformity, extrusion of brain, harelip, cleft palate and eye defects. 100,000 to 200,000 units of vitamin A daily will reduce the number of sperm and their motility.

VITAMIN B-2, RIBOFLAVIN. Pregnant mothers on a riboflavin deficient diet can give birth to neonates with such abnormalities as: shortened mandible, Robbin's syndrome (micrognathia, glossoptosis), protruding tongue, anterior tapering of nasal part of face, shortened nose, poor development of maxilloturbinals, reduction in number of naso-turbinals, cleft palate, smaller nasal chamber in region of ethmoturbinals but larger anteriorly, and shortening of limbs.

When the maternal riboflavin deficiency is experimentally accentuated by the addition of the antimetabolite galactoflavin, then results are more serious. There occurs a high incidence of fetal death, or, congenital anomalies including abnormalities of the skeleton, urogenital system, cardiovascular system, cerebrum, eyes, and herniations of the diaphragm and body wall.

VITAMIN B-3, PANTOTHENIC ACID. Pantothenic acid deficiency in the diet of the pregnant mother may result in small litters, undersized young, accumulation of pyruvic acid in the fetus, diminution of alkaline phosphatase in adrenals of young at birth, exencephaly, anophthalmia, oedema, redness and irregular swellings at distal ends of limbs, arrest of circulation in dilated marginal veins of the limb, disappearance of vascular endothelium, coagulation of blood with tissue degeneration, distortion of skeletal elements, epidermal degeneration, hemorrhage and amputations.

When the deficiency is accentuated by the addition of the antimetabolite omega-methyl-pantothenic acid, then the defects include cerebral and ocular deformity, digital hemorrhages and oedema, interventricular septal defects, anomalies of the aortic arch patterns, hydronephrosis, hydroureter, club foot, tail defects, cleft palate and dermal defects.

VITAMIN B-6, PYRIDOXINE. Vitamin B-6 deficiency during pregnancy reduces the serum protein and non-protein nitrogen of the serum to levels similar to those reported for the toxemias of pregnancy. It has been shown that sufficient B-6 in the diet BEFORE mating is as essential as sufficient in the diet DURING gestation.

VITAMIN B-9, FOLIC ACID, PTEROYLGLUTAMIC ACID. Pregnant mothers on diets deficient in B-9 present embryos and neonates with the following types of abnormalities: absence of kidney, renal ectopia, renal hypoplasia or retardation of kidney development, hydronephrosis, ureteric ectopia, atresia of intermediate portions of the ureters, hydroureter, obliteration of cranial portion of ureter, persistently closed ureteral orifices, urethral stenosis, congenital skeletal abnormalities with retarded ossification in some areas, ossification absent in others, and malformation of ossified skeletal elements.

When this deficiency is reinforced with succinylsulfathiazole and a crude PGA antagonist, then the embryos die early and are resorbed, or marked oedema occurs, also anemia, cleft palate, syndactylism, retarded lungs and kidneys, Morgagnian-type cataracts; anomalies of the nervous system, eyes, respiratory system, diaphragm and cardiovascular system.

When the Folic acid antagonist, 4-amino-pteroylglutamic acid is orally administered to the pregnant mother, then fetal death may occur with abortion. The young fetuses show liver necrosis, adrenal necrosis, depression of hemopoiesis, necrosis of intestinal epithelia and cranial malformations.

VITAMIN B-12, COBALAMIN. Deficiency of dietary B-12 produces in the embryos and fetuses such pathological conditions as hydrocephaly; cerebral aqueducts which may be closed, constricted or of abnormal shape or size; partial or complete loss of ependymal cells of third ventricle; absence of special groups of cells in the roof of the aqueduct and ventricle; enlarged thyroid; edema; fatty heart, liver and kidney; and hemorrhage of yolk sac. B-12 is also related to the storage of Folic acid in the egg yolk. A deficiency of Folic acid and Riboflavin coupled with a B-12 shortage, leads to defective cartilage and phosphatase formation and a lower rate of ossification; low phosphatase formation means low phosphorus deposition.

VITAMIN B-1, THIAMINE. This vitamin is needed to maintain the seminiferous tubules of the testis. B-complex vitamins bring improvement in conditions of oligospermia and are needed to maintain the accessory reproductive structures -- the prostate, and seminal vesicles. (We most frequently hear of B-1 deficiency in connection with the disease of the nervous system called beriberi. The earliest reference to beriberi is also found in the oldest medical treatise extant, called the NEICHING, attributed to the authorship of Hwanti, and dated 2,697 B. C.).

VITAMIN C. Adequate vitamin C is important in preventing miscarriage, especially in women 40 years of age and over. 500 mg of ascorbic acid daily along with a high intake of citrus fruit and 5 mg of vitamin K (daily) will prevent decidual hemorrhage from leading to pathological abortion.

When vitamin C is administered during pregnancy, there is a fall in antibody titre showing that this vitamin has a neutralizing effect upon agglutinins. This being so, Rh-positive infants may be delivered normal with negative Coombs test and with no signs of erythroblastosis fetalis. In a deficiency of vitamin C, the erythroblastosis may take its toll and cause brain damage and malformation consequent to oxygen deprivation.

Vitamin C administration in the male increases sperm motility and a disappearance of abnormal forms. In a deficiency of C, there may be a sloughing of the immature spermatids into the epididymides.

VITAMIN D. Vitamin D in average doses will bring improvement from conditions of oligospermia, but larger doses will cause azoospermia.

Excess vitamin D may be involved along with excess vitamin A in acute hydrocephaly with vomiting. Excess vitamin D in the newborn and young can cause death with metastatic calcification and the synthetic forms are more dangerous than the natural forms of D. Excess D taken by the pregnant mother can lead to calcification of the placenta and abortion, along with renal damage to the young, with hematuria.

VITAMIN E. A deficiency in this vitamin may be serious for the developing embryo. Defects include blindness, cloudy lens, cloudy spots under the cornea, smaller body size than normal, microcytic anemia, low reticulocyte count (E is needed in hemopoiesis), disturbances of uterine implantation, low fecundity, death of embryos, resorption, retarded differentiation of mesenchyme into connective tissue fibroblasts, overproduction of collagenous fibers, adipose metamorphosis of new connective tissue (prompted by diets rich in saturated triglycerides), decrease in elastic fibers of the heart, renal autolysis, and muscular degeneration (vitamin E and sulphur deficiency).

Vitamin E administration can increase the number and motility of sperm and cause abnormal forms to disappear. Prolonged E deficiency leads to irreparable injury to the testis and the seminiferous tubules degenerate.

There is evidence that the turkey hen stores vitamin E, that E-deficiency diminishes hatchability and that additions of E to the diet increases hatchability from a low of 52 per cent up to 88 per cent.

FATS and FATTY ACIDS. Females grown to maturity on a fat free diet will breed but give birth to dead young, or young which die soon after birth; the deficiency in arachidonic acid is critical. Fat deficiency in growing animals also leads to pathology of the brain, liver, heart, kidney, thyroid and skin; body weight will also suffer.

SUCROSE. The addition of sucrose sugar to commercial rations will result in a larger number of young which are also heavier at birth; sucrose improves lactation and increases weanling weight.

PROTEIN. Animals on a protein-free diet will have a 90-100 per cent resorption of the young. Both the amino acid methionine and the vitamin Pantothenic acid are necessary to maintain normal Coenzyme A levels. The requirement for the amino acid DL-trytophane is increased when the vitamin Nicotinic acid is absent from the diet.

CALCIUM and PHOSPHORUS. A high calcium to phosphorus ratio will increase the incidence of skeletal anomalies. Calcium is needed for uterine inertia at labor and parturition; it enhances the effect of oxytocin. Both operate together in preventing post-partum hemorrhage.

MANGANESE. Since manganese is needed in bone formation, deficiencies in this metal result in leg abnormalities (slipped tendon, perosis in fowl), poor hatchability and abnormal chicks; young rabbits develop crooked bones in manganese deficiency states.

IODINE. Deaf-mutism may be a congenital defect. There has been a marked decrease in the number of deaf-mutes due to goitre prevention with iodized salt.

POTASSIUM. In a dietary deficiency of Potassium, Thiamine, Pyridoxine and Protein, the maternal organism is affected with diminished output of estrogen and progesterone hormone. In these four deficiencies, fetal death occurs. But death can be prevented and with no congenital abnormalities, and pregnancy maintained, by daily injections of estrone and progesterone.

At several places we made reference to vitamin antagonists and analogs, and in passing, a few more comments are given. These vitamin analogs act in enzyme systems and metabolism, and malformation in mammals and other vertebrates have been reported as resulting from the action of analogs of Thiamin, Riboflavin, Niacin, Folic acid, Pyridoxine, etc. For example, sulfanilamide is an analog of p-aminobenzoic acid, glucoascorbic acid for ascorbic acid, ureylenecylohexylvaleric acid for biotin, hexachlorcyclohexane for meso-inositol, triethyl analog for choline, pantoyltaurine and beta-pantoylaminoethamethic for pantothenic acid, 3-acetylpyridine for nicotinic acid, deoxypyridoxine for pyridoxine, isoriboflavin for riboflavin, dicoumarol for vitamin K, alpha-tocopherol quinone for alpha-tocopherol (interruption of pregnancy and embryo resorption), and 4-10 mg of x-methyl folic acid antagonist will cause resorption or abortion in man. There are some 7 analogs of pteroylglutamic acid as follows: 9-methyl, 10-methyl (Methopterin), 9,10-Dimethyl, 4-Amino (Aminopterin), 4-amino-9-methyl (A-ninopterin), 4-amino-10-methyl (Amethopterin) and, 4-amino-9,10-dimethyl (A-denopterin). There are also four or more analogs and related compounds of vitamin B-12.

We should include some explanation of the biochemical functions of the vitamins, since in so doing, we may better understand how deficiencies in these metabolites can lead to structural defect, malfunctioning, disease, and even death. Vitamins are integral parts of Coenzymes and so function. They are therefore effective in small amounts; they catalyze reactions. Being associated with enzymes, they are necessarily tied up with protein, since enzymes are proteinaceous. We know for example, that vitamin K, a fat-soluble member of the vitamin B complex, is an essential unit in the structural configuration of Prothrombin, vital in the blood clotting reaction.

Since this subject is indeed vast, our discussion is arbitrarily limited to the biochemical functions of certain B-vitamins. Nicotinic acid (or Nicotinamide) is incorporated as a part of Coenzyme I and Coenzyme II which in turn are involved in some 48 different enzyme systems carrying on oxidation and reduction reactions. Two vitamins, Thiamine (B-1) and Lipoic acid, combine and so comprise the Coenzyme Cocarboxylase involved in at least 6 vital reactions. Only the dextro-rotatory form of Pantothenic acid has vitamin activity; this B-vitamin is a structural unit in Coenzyme A essential in the oxidation of fat, of amino acid carbon residues, and of pyruvate and alpha-ketoglutarate. Both the free vitamin Lipoic acid, and the Lipothiamide pyrophosphate have Coenzyme functions, involved not only in photosynthesis but in the oxidative decarboxylation of pyruvate and alpha-ketoglutaric acid, and in growth promotion of chicks and rats wherein 10 to 1,000 micrograms are effective. In the oxidation of pyruvate, the four B-vitamins, Thiamine, Lipoic acid, Pantothenic acid, and Nicotinamide, are all involved. Riboflavin (B-2) is a part of the Coenzymes Riboflavin phosphate (Flavin mononucleotide) and Flavin adenine dinucleotide, which carry on in some eight oxidation reactions. Vitamin B-6 (Pyridoxine) is integrated into two Coenzymes, Pyridoxal phosphate and Pyridoxamine phosphate, which in turn are involved in the decarboxylation of six different amino acids, in three transamination reactions, and in the reactions of certain (two) beta-methylene groups. The vitamin, Biotin, is part of Coenzymes involved in the formation of acetoacetate from isovaleric acid -- a reaction involving Carbon dioxide fixation in animals, plants and micro-organisms. Animals deficient in Biotin show an increase in urinary Ammonia. Oxalacetic decarboxylase concentrates of liver contain Biotin (after hydrolysis).

Since then, these many reactions must occur in order to carry on life processes in an embryo, and to elaborate its bulk and configuration, it is easily seen how specific nutrient deficiencies can lead to morphological aberrations and malfunctioning.

Our view is further emphasized by a quotation from Woolam and Millen in the British Medical Journal, vol. 1, for June 2, 1956 (abstract in JAMA 162(5):516, September 29, 1956): "The increased demand by the pregnant woman for vitamins reflects the need of the embryo to build up a store of these substances, and experiments with animals indicate that if the minimum requirement is not met the embryo will either die or be born congenitally

deformed.....Minor degrees of experimental vitamin deficiencies produce malformations during the early months of pregnancy. The results of the experiments.....suggest that the only way in which the nutrition of the embryo can be safe-guarded is by attention being directed toward the diet(s) of woman (women) throughout their lives, and especially of girls in the later stages of adolescence. Only by reorienting our attitude in this way can we ensure that the members of the next generation will develop in bodies that provide an adequate supply of essential foodstuffs from the beginning of pregnancy."

Even fasting on the part of the pregnant mother can lead to developmental anomaly in the unborn, particularly in the very early days of pregnancy. Runner and Miller (1956) demonstrated in rats, a consistent pattern of defects in vertebrae, ribs and cranium, a relatively narrow interval in which the embryo is affected, and the almost complete protection by small quantities of carbohydrate or amino acids.

Iago Galdston has this to say: "Since all adult humans have developed some degree of deprivation, the embryo is subject to this deficiency throughout the critical period of formation as well as the later period of growth and development both intrauterine and extrauterine. Any stress applied during these periods further increases the requirements, and if the supply is inadequate, the result is further maternal deprivation and a conditioned deficiency in the offspring. The uncompensated stresses of infancy and childhood further increase the degree of deficiency and the individual enters the childbearing period in a status less than optimum. Childbearing covers a period of approximately 35 years, adding residual damage as this period progresses. The less efficient an individual's physiologic and metabolic level, the less will be her ability to respond favorably, because of the prolonged alterations of all vital functions (in pregnancy). The fact that major and minor disturbances do occur during pregnancy, like nausea and vomiting, easy fatigability, psychological instability and many subjective symptoms does not in any way establish that they are necessary or desirable. They are the result of complex, closely interrelated dysfunctions of the individual patient's metabolism and physiology; or, in brief, alterations in nutrition as the result of deprivation and stress."..... "Toxemia symptoms are associated (toxemia of pregnancy) with the level of total serum protein and serum albumin. Albumin is used and is made up by increased production of globulin for blood level. Protein deficiency can cause toxemia of pregnancy. Also, overweight at the beginning or gaining excessively during pregnancy increases the incidence of toxemia of pregnancy; underweight causes twice as much toxemia. Deprivation must be recognized early in pregnancy and remedial procedures begun immediately. Delays seriously increase the hazards to mother and child. Those who got both vitamin and protein therapy resulted in only 1/6th having pre-eclampsia. Underweight is a great obstetrical hazard, leading to toxemia and premature labor."..... "The pregnant mother needs extra calories to spare the conversion of protein for energy needs; thus tissue integrity is protected. All patients should

receive vitamin supplementation to avoid a further depletion of these critical elements and to increase the absorption and utilization of the dietary essential nutrient intake."....."Food fads and prejudices result in the elimination of foods containing essential nutrients."

Early infancy is so closely related in time to gestation, that it would be well to quote Platt on the relation of infant feeding and diseases in later life. Prof. Platt of the Human Nutrition Research Unit (England) has pointed out that errors in infant feeding might be the cause of disease in later life, according to the B.M.J. 1:179, 1955. And in the JAMA 158(6):497, for June 11, 1955, we find the following from Platt: "In western countries many infants are never breast fed, or, if they are, weaning takes place early. Chemically there is an appreciable difference between human and cow's milk. There is, for example, six times as much calcium in cow's as in human milk, and this might well be a cause of hypercalcemia. Cow's milk, on the other hand, contains less lactose than human milk. Galactose, which is derived from lactose, is an essential constituent of the cerebrosides of the central nervous system and the mucopolysaccharides of connective tissues. Myelinization of nerve tissue continues until the fifth or sixth year of life. Platt suspects that when an infant is artificially fed on a "humanized" cow's milk preparation, which may supply only a third as much galactose as human milk, the composition of myelin may be affected. If insufficient galactose is available, cerebrosides containing glucose are formed in the body of the experimental animal. If such abnormal cerebrosides are present in the myelin of the infant, this might affect the subsequent health of the child. Galactose deficiency, with a change in the composition of myelin, may play a part in the cause of multiple sclerosis. In communities where breast feeding is usual, multiple sclerosis is rare, and where large quantities of carbohydrate are consumed in infancy, as in the West Indies, nervous diseases such as transverse myelitis are common. Animal experiments have shown that deficiency diseases in infancy, or even in utero, may affect the animal in later life. We may be reaping in medical practice and in the postmortem room today the errors of infant feeding methods that were prevalent 20 to 30 years ago. Galactose is also a constituent of some components of ground substance and connective tissue; with glucose and mannose it is an integral constituent of the reticular fibers of connective tissue. The presence of galactose in collagen has been reported, and it has been claimed that there is some abnormality in this constituent in the collagen diseases. The artificial feeding of infants results in a deficiency of galactose, which may affect the nature, composition, and reaction to stress in later life of the extracellular matrix and connective tissue."

On the subject of developmental defect prevention, Ingalls (1956) has this to say: "Congenital defects are not all genetically determined at the moment of conception: many are acquired during the ensuing fetal development. The latter are usually fetal manifestations of critical stress on the mother during pregnancy. Just as the genetically determined defects have been studied in the fruit fly by breeding experiments, so the acquired defects have been

studied in the gravid mouse by using hypoxia as a standard stress at different stages in gestation. From these latter experiments a whole panorama of deviations emerges, determined as to kind and severity by the timing and degree of the stress applied to the mother. A large class of congenital defects is therefore preventable. They need to be attacked with the same energy that is now being directed at poliomyelitis and other causes of disability.

We must emphasize the importance of the time of instituting the deficiency during pregnancy, the briefness of the period necessary to affect embryonic development, and the irreversibility of fetal damage by vitamin supplementation later in pregnancy. The earlier stages of embryonic development are more severely affected by the same length of deficiency than the later stages. And it is not so much the quantity of food as it is the quality which must be emphasized. Quantity in excess can be damaging, and the administration of vitamins and minerals must be in PROPORTION to the rest of the nutritional intake.

(Admiral Dewey, hero of Manila Bay, enjoyed splendid health. Once when complimented on his superb physique he smiled and said: "I attribute my good condition to plenty of exercise and no banquets. One-third of what we eat, you know, enables us to live." "In that case," he was asked, "what becomes of the other two-thirds?" "Oh," replied the Admiral, "that enables the physician to live.")

There can be no compromise in the provision of a proper, complete and wholesome nutrition. J. Douglas Thompson observed: "Nature originally meant for her inhabitants to eat food as she produced it, without alteration or cooking. But man knew better." And, as St. Louis A. Estes said: "The Almighty has made no mistakes in the formation of our bodies-----medical philosophy to the contrary notwithstanding."

(There can be no straddling of the fence in this matter as is done in political Mississippi which has a squirrel law with half the people for it and half of them against it. During a certain political campaign down there, one of the candidates made a big speech and at the finish said, "Now does anyone have any questions?" One in the crowd said, "Yeah, how do you stand on the squirrel law?" The candidate thought for a moment and replied, "Glad you asked me that question. I understand half my friends are for it, and half against it. I want it clearly understood that I'm for my friends.")

It is a never ending an ever compromising battle to provide proper food, and eternal vigilance is the price of any success. But it should give us heart that it has ever been thus in matters of struggle in all areas of constructive human endeavor. (Even Virchow, who was the father of pathology, quarreled endlessly with Bismarck, agreeing only once with the Iron Chancellor when engaged in an issue against the Catholic church. Bismarck at last challenged Virchow to a duel. Virchow replied that since he was the one challenged, he also had the choice of weapons. Accordingly, Virchow exhibited two sausages,

one loaded with Trichina, and asked Bismarck to choose first. Bismarck decided to laugh the matter off.)

(This incident had its imitation in England between Gladstone and Disraeli, who eventually served as prime ministers in the order mentioned. William Gladstone was Disraeli's chief rival in the parliament, and the two were constantly engaged in verbal jousts: On one occasion Gladstone shouted: "Disraeli, you will come to your end, either upon the gallows, or from some loathsome disease." Disraeli replied: "That depends on whether I embrace your principles, or your mistress.")

(There is also the story of a British officer, jealous of Putnam, famous officer during the French and Indian war. When the British officer received no answer from Putnam to his challenge, he went to Putnam's tent and found him sitting on a keg smoking a pipe and demanded an explanation of him. "Well," said Putnam, "I have never been good at firing pistols. If we fight with them, you will have an unfair advantage. Here are two powder kegs. I have bored a hole and inserted a small fuse in each. So if you will be good enough to sit down, I will light the fuses, and he who dares sit the longest shall be called the bravest." The fuses burned slowly, and the British officer was nervous and jumpy. When the fuse burned down to within an inch of the kegs, the English officer jumped up and ran..... The kegs were full of onions.)

Before bringing this discussion to an end, it would be pertinent to include a little information on the general topic of diet and life span. The information which follows is taken from JAMA 158(15):1402-3, for August 13, 1955 and is an abstract of a paper by M. Silberberg and R. Silberberg in Physiol. Rev., 35:347-362, for April 1955. "The duration of life is determined by the interaction of genetic and environmental factors, both of which influence the rates of growth, development, and aging. Environment may permit the intrinsic life potential to assert itself to the fullest extent or may increase the hazards to life and this cause premature death. Dietary influences may exert both kinds of effects by affecting the course of disease as well as the processes of growth, development and aging. In a variety of lower animals, life may be prolonged by restriction of food. This is associated with far-reaching reduction of body size, vital activities, or both to which these species can adjust themselves. Higher species with their complex organization, however, are, particularly during the period of growth, less adaptable to drastic food restriction than the lower animals. Moderate dietary restriction favors longevity during certain periods of life. The exact age at which restriction should be instituted in order to accomplish an optimal effect has yet to be determined. In mammals this date may coincide with the stage of development of the long bones when regressive changes begin to overcome the growth of the epiphysial cartilage. Although there is no evidence that under these conditions the absolute life span can be prolonged, the average duration of life may be increased either by prevention of disease or by retardation of age changes or both. Severe

underfeeding immediately after weaning is incompatible with normal growth and development and may even result in increased mortality early in life, particularly in girls, but the mortality of surviving persons is decreased, and some survivors will live to extreme old age. This induced longevity, however, does not prove that under-nutrition so drastic as to cause stunting of growth is desirable from a biological point of view, Large dietary protein or carbohydrate allowances apparently do not worsen the prospects as to longevity provided no secondary deficiencies will be created. A high level of dietary fat has, as a rule, adverse effects on the life span. Apparently somewhere between the extremes of undernourishment and dietary enrichments lie those regimens that are optimal for longevity. Ideally, these should permit a good and uniform but not necessarily fast rate of growth and development early in life, and should, in order to avoid the injurious effects of overnutrition, subsequently stay at a low level that should still be adequate to permit a person to live not only a long but, at the same time an active and useful life. Retardation of growth as such does not appear to contribute materially to the shortening of the life span. On the other hand there are indications that the duration of life is influenced more by conditions to which the effect on growth is incidental and which prevail also when growth has passed its most active phase. This agrees with the concept that growth and longevity are not mutually inter-dependent but are coordinated phenomena governed by the same metabolic principles."

In closing, I would like to comment with Thomson that "This paper will no doubt be found interesting by those who take an interest in it."

Reprint No. 66B

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