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Maternal nutrition in relation to abnormal foetal development

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During the first 9 months of his existence, man's life hangs almost literally by a thread —the thread which connects him to the mother who not only breathes and excretes for the foetus but also digests food and furnishes nutriment for the growth of the new individual.

In this period of intra-uterine development in which the individual changes from a single cell to a complex creature of 200 billion or more cells, he is exposed to the influence of two principal factors: heredity and environment. The first of these, the hereditary factor, is already determined at the fertilization of the ovum, and there is, as yet, no evidence that it can be altered by any form of treatment, and although selective breeding is extensively practised in animals, the human population, despite the wishes of eugenists, is strongly resistant to restrictions applied to its mating habits. The second factor, the environment, is, however, of almost equal importance in the development of the foetus.

The environment of the foetus is its mother, and the development of the foetus is strongly influenced by nutritional factors which themselves reflect with considerable exactitude the state of nutrition of the mother.

The processes of nutrition, the term being used in its widest sense, comprise the ingestion of foodstuffs (including vitamins and trace elements) and their digestion, absorption and utilization, and the inspiration of oxygen and the expiration of carbon dioxide. The state of nutrition can also be influenced by the effects produced by the invasion of pathological organisms or by alterations in the hormonal, nervous or psychic balance.

The two sources of information concerning the effects of dietary and metabolic errors during pregnancy are studies carried out on the human population and animal experiments. Although it is from animal experiments that the mass of evidence that dietary errors can result in the production of congenital malformations has been obtained, a certain amount of information has been brought to light on

the effects of maternal nutrition in the production of deformities in man. This information is difficult to interpret because of the many variable factors that have to be taken into account. To give but one example: although the quantity and nature of the food consumed in the home of a pregnant woman may be nutritionally more than adequate, the woman herself may not be consuming a proportionate amount of this food, or may, having ingested it, fail to digest, absorb or utilize the food. To assess her nutritional state on the basis of the food available in the home may lead therefore to erroneous conclusions.

Nevertheless it is worth noting that a number of reports have appeared which support the view that a low level of intake of the basic foodstuffs during pregnancy, with presumably some degree of associated vitamin deficiency, is associated with an increased incidence of congenital malformations. The carefully documented studies on the incidence of anencephaly carried out by Coffey & Jessop (1958) in Dublin have shown a relationship between the occurrence of this malformation and a poor state of maternal nutrition. Again Anderson, Baird & Thomson (1958) concluded from their work that 'primigravidae living in poor social circumstances have a higher risk than any other group of pregnant women of foetal death due to malformations of the central nervous system'. On the other hand Record & McKeown (1949) found no association between the incidence of malformations of the foetal central nervous system and the housing of the mother, and Edwards (1958) studying the incidence of similar deformities in Scotland noted that although there was a higher incidence in the lower social class, there was no decline in the incidence with the onset of the present period of generally improved nutrition.

The bulk of our information has therefore of necessity come from animal experiments. Somewhat surprisingly, there are few reports of the effects of total starvation during pregnancy on the incidence of abnormal offspring in experimental animals. Runner & Miller (1956), however, produced congenital malformations in mice by starving the pregnant animals for 24 h during the 8th or 9th day of pregnancy.

Much of our present knowledge deals with the influence of vitamin deficiency or excess in the production of congenital malformations. In this regard most interest perhaps attaches to the role of vitamin A. The induction of a state of hypovitaminosis A during pregnancy has been shown to result in the production of a wide range of malformations in the pig, rabbit and rat. Among the malformations produced in this way are anomalies of the eyes ranging from anophthalmia to microphthalmia (Hale, 1935; Warkany & Schraffenberger, 1944), abnormalities of the urogenital system including horseshoe-kidney and failure of the testes to descend (Wilson & Warkany, 1948), diaphragmatic hernia (Anderson, 1949) and hydrocephaly (Millen, Woollam & Lamming, 1953; Rokkones, 1955).

It is of interest to note that vitamin A is, up to the present, the only vitamin of which an excess has been shown to have a teratogenic effect in pregnant animals. The first report of the effects of hypervitaminosis A during pregnancy appeared 6 years ago when Cohlan (1953) showed that malformed young were present in the litters of rats that had ingested large amounts of vitamin A during pregnancy. Among the abnormalities which he noted were hydrocephaly, exencephaly, spina bifida and

cleft palate. Cohlan's observations have since been amply confirmed by other workers, though hydrocephalus appears to be an infrequent finding (Giroud & Martinet, 1954; Millen & Woollam, 1957; Warkany, Kalter & Geiger, 1957; Woollam & Millen, 1957).

Deficiencies during pregnancy of vitamins other than vitamin A also result in the birth of malformed young. The most exhaustively studied deficiencies have been those of members of the vitamin B complex. Hypovitaminosis has been induced by a deficient diet either alone or in combination with a vitamin antagonist. By this method it has been shown that abnormal young can be produced by deficiency of riboflavin (Warkany & Nelson, 1940; Giroud & Boisselot, 1947; Grainger, O'Dell & Hogan, 1954), of pantothenic acid (Boisselot, 1948; Nelson, Wright, Baird & Evans, 1957) or of folic (pteroylglutamic) acid (Richardson & Hogan, 1946; Giroud & Lefebvres, 1951; Nelson, Wright, Asling & Evans, 1955). Experiments have indicated that a deficiency in any one of these substances results in abnormalities of the brain, including hydrocephaly and anencephaly, defects in the development of the eyes, cardiovascular and urogenital anomalies and skeletal defects including cleft palate.

Cheng & Thomas (1953) have been able to produce a similar range of malformations by the use of a vitamin E-deficient diet.

Derangements of normal metabolism may occur either through a natural or an experimentally induced hormonal deficiency or by the administration of hormones in excessive quantities during pregnancy. Gross hormonal disturbances during pregnancy in man probably result in abortion, but probably of more importance from the standpoint of malformations are disorders of less severe degree or of short duration, which may be overlooked.

Hoet, Brasseur & de Meyer (1955) have drawn attention to the relationship between a reduced glucose tolerance in pregnancy, not amounting to clinical diabetes, and the occurrence of congenital malformations in man. The need for caution in the administration of cortisone during early pregnancy is suggested by the report of cleft palate in a child whose mother had been treated with cortisone (Harris & Ross, 1956). The association between naturally occurring thyroid deficiency during gestation and cretinism is too well known to require further comment. Experimentally, Langman & van Faassen (1955) have shown that partial thyroidectomy carried out in female rats shortly before pregnancy will result in the birth of young with cleft palates and eye deformities.

It has been shown experimentally that administration of cortisone increases the incidence of cleft palate in a genetically susceptible strain of mice (Fraser & Fainstat, 1951), and cleft palate has also been produced in rabbits by the injection of cortisone during pregnancy (Fainstat, 1954). The injection of insulin into pregnant animals may also provoke the appearance of malformations in the young. Smithberg, Sanchez & Runner (1956) were able to produce exencephaly and skeletal deformities in mice by this method, and malformations have also been induced in rabbits (Chomette, 1955; Brinsmade, 1957).

An interesting line of research has been opened up by the discovery that the incidence of congenital malformations produced experimentally by hypervitaminosis A can be influenced by the concurrent administration of hormones and antihormones.

It appears from experiments carried out by us that though the concurrent administration of some substances has an augmenting or synergic effect on the incidence of abnormal young produced by hypervitaminosis A, other substances exert a protective effect. In experiments in which cortisone was given in addition to vitamin A there was an increase from 7·8 to 36·6% in the number of young with deformities of the brain and skull (Millen & Woollam, 1957) and from 29·7 to 100% in the number with cleft palates (Woollam & Millen, 1957). Treatment with methylthiouracil in the drinking water resulted in an increase to 68·8% in the number with malformations of the head (Woollam & Millen, 1958). On the other hand, the concurrent administration of thyroxine in one group of experiments, prevented the deformities due to hypervitaminosis A (Millen & Woollam, 1959). In another series, vitamins of the B complex were given at the same time as vitamin A and the incidence of young with cleft palate fell from 31·4 to 1·4% (Millen & Woollam, 1958*a*). Protamine zinc insulin administered concurrently with vitamin A and cortisone appeared to protect the young against the augmenting effect of the cortisone. Instead of an increase in the number of young with brain deformities there was a reduction to 1·2% (Millen & Woollam, 1958*b*).

Many lines of thought are suggested by these experiments. Is the effect of a hypervitaminosis A to produce a relative deficiency of other vitamins by displacement? Cortisone and insulin have important relationships to carbohydrate metabolism. Could it be that the basic defect in teratogenesis is an error in the metabolism of carbohydrates that is insufficient to manifest itself clearly on clinical examination? Certainly the observations of Hoet *et al.* (1955) on the association between a prediabetic condition during pregnancy and the occurrence of foetal malformations would support such a possibility.

This review of the relationship between maternal nutrition and abnormal foetal development has of necessity been both brief and compressed. There are two points that seem worth making in summing up. The first is the need for further investigation, from the clinical standpoint, of maternal nutrition during pregnancy, with particular emphasis on the possible importance of minor degrees of vitamin deficiency in the first 3 months of pregnancy. The second is the value of the teratogenic experiment as a test-tube, as it were, in which the interaction of vitamins and hormones may be studied. The solution of many other pressing clinical problems may well come from the elucidation of the problem of congenital malformations, and from the direction of our attention to some extent away from three score years and ten and towards that period when, in the words of Sir Thomas Browne (1643), 'we live, move, have a being, and are subject to the actions of the elements and the malice of diseases in that other world, the truest microcosm, the womb of our mother'.

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Body stores in human pregnancy and lactation

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It is generally believed that, in man as well as in animals, metabolism during pregnancy is strongly anabolic, storage tending to exceed the amount attributable to the growth of the product of conception and the enlargement of the organs of reproduction. The surplus is usually interpreted as a reserve for lactation, in which the trend is believed to be katabolic. But the evidence for man is scanty, and the great variation of the gain in body-weight in human pregnancy suggests that there must be many exceptions.

Metabolism during pregnancy

There was originally some controversy about the extent to which foetal growth depends on the adequacy of the diet taken by the mother, but most authorities now