15 are in complete remission and not taking neostigmine at the time of writing, and 9 others (a total of 24, or 55%) have transient or minimal ocular symptoms only.

TABLE III.—*Contemporary Assessment of the Series*

Group 1 (minimal or no disability)	24
" 2 (slight disability)	13
" 3 (moderate ")	7
" 4 (severe ")	0
Dead	9
Not traced	7
	60

Group 1 = Normal activity with minimal, transient, or no ocular symptoms. Group 2 = Slight tiredness or more prolonged ocular symptoms. Group 3 = Unable to work or do housework but still ambulant. Group 4 = Bedridden, in hospital, or unable to walk.

Summary

Myasthenia gravis is an uncommon disease, but its incidence is at least 1 in 40,000 of the population, and there are probably at least 2,000 examples in Great Britain at any one time.

The records of 60 patients (25 males and 35 females) personally observed over the period 1934–55 have been analysed.

The age of onset of symptoms varied from 6 to 75 years, being between 21 and 50 in 65%.

The diagnosis is frequently overlooked in the early stages, especially when there is a monosymptomatic onset.

Twelve patients had purely ocular symptoms throughout; conversely, in only five was there no history of ocular symptoms.

The disease is characterized by daily fluctuations as well as by partial and complete remissions, sometimes for long periods. In this series 50% at no time had had a complete remission.

The shortest history in a fatal example was one year. The longest history of continuing symptoms was 28 years.

The discovery of neostigmine has revolutionized the treatment and prognosis of the disease; very large doses can apparently be taken for an indefinite period, the highest dosage in this series being 600 mg. a day for 20 years. Personal experience of other methods of treatment (including thymic irradiation, thymectomy, and the use of pyridostigmine) is too small from which to draw conclusions.

The mortality in medically treated patients is still probably not less than 20%.

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ROLE OF VITAMINS IN EMBRYONIC DEVELOPMENT

BY

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The therapeutic value of vitamins has been the subject of some scepticism in recent years. To some extent this represents a normal and healthy reaction to the extravagances of the immediate pre-war period when, as Christian (1947) put it, there arose "between the clinic and the advertising world . . . an hysteria about vitamins and other factors of nutrition with many wild statements often not properly restrained by those with medical training." It is now generally recognized, however, that the vitamins are not drugs to be abandoned because they fail to cure certain diseases; they are essential food factors, and unless they are present in our diet we die.

Requirements during Pregnancy

During certain periods of life there is an increased demand on the part of the body for vitamins. The most important of these periods is pregnancy. From the original observations that beriberi and night blindness occurred more commonly in pregnant women, it has gradually become recognized that there is an increased requirement for all the vitamins during pregnancy. Some obstetricians are even inclined to attribute some of the common disorders of pregnancy, such as uterine haemorrhage, to vitamin deficiency (McIlroy, 1935). Be that as it may, in recent years the supplementation of the diet of the expectant mother with an adequate supply of vitamins has become a recognized feature of antenatal hygiene. There is a possible danger that, with the increasing scepticism concerning the value of vitamins, this precaution may cease to be taken.

The tendency has been for apologists for the administration of vitamins during pregnancy to stress the significance to the mother of hypovitaminosis at this critical time. A great deal of work has now been performed which shows that, in experimental and domestic animals, an adequate supply of vitamins is of the utmost importance to the developing embryo. This side of the picture has been somewhat neglected, and it is the object of this paper to draw attention to what may happen to the developing foetus if its mother is not in receipt of an adequate supply of vitamins, or is in a state of vitamin deficiency when she conceives.

A vitamin deficiency can affect the foetus in two ways, depending on the stage of embryonic development at which its effects are felt. During the early period of pregnancy a single fertilized cell changes into a complex multicellular organism. In this "period of differentiation" the various organs are built up to what is virtually the adult pattern. The later period of pregnancy is devoted to growth in size, and this growth continues without a break after birth. Generally speaking, therefore, the effect of a vitamin deficiency during the first stage (corresponding to the first three months of pregnancy in the human) will be to interfere with the development of vital organs, such as the heart and the brain, which are then in a critical stage of their development. The result will be the birth of a foetus with a congenital malformation which represents a form of arrested or abnormal growth. If the effect occurs in the later period of pregnancy it will fall on tissues which behave as do those of the adult, and if any lesions are produced they

The Government of Iraq has notified the World Health Organization of its intention to contribute a sum of \$4,200 to the World Fund for Malaria Eradication. This is the fourth contribution to this voluntary fund, previous gifts having come from Brunei, China, and the Federal Republic of Germany.

will resemble those seen in adults suffering from deficiency of that vitamin. In practice, the division between these two possible phases of action does not turn out to be so clear-cut, since differentiation is not entirely restricted to the earlier period, and some tissues, notably the bones, which undergo considerable postnatal developmental changes, react to vitamin deficiencies in both ways.

The effect of a gross vitamin deficiency is to cause cessation of growth and death of the embryo. The effect of a less severe deficiency acting on an organ in a critical phase of differentiation is to arrest the development of that organ either wholly or in part. The deformity produced will depend largely on whether the interference is with the formation or the elimination of an element of that organ. A cleft-palate, for example, is produced by a failure of fusion of two elements which normally meet in the roof of the mouth. An abnormal communication between two chambers of the heart may result from an interference with the growth of the partition which normally separates the two chambers. On the other hand, an imperforate anus results from failure of breakdown of the membrane which in foetal life separates the intestine from the surface.

From knowledge of the times of normal development, it is possible to deduce what time during gestation each process went astray. It does not necessarily follow, however, that this time corresponds to the time at which the interference with the process of development took place. For example, the ductus arteriosus, which enables deoxygenated blood to by-pass the lungs in the foetus, normally closes at birth. This channel may remain open as a congenital abnormality. From experimental work and from observations upon human cases it is known that this abnormality may be determined by events which take place in the second month of pregnancy. All that can be said with certainty is that any agent which is capable of provoking such an abnormality must do so *before* the time when the developmental process with which it interferes normally takes place. How long before, it is never possible to say. Since the critical phase of human development is, for most organs, within the first three months of pregnancy, it is clear that if vitamin deficiencies interfere with normal development the mother must have a good store of vitamins *before* she conceives. The administration of a large supply of vitamins once pregnancy is established can never be an adequate substitute for a good nutritional status at the time of conception.

All our information on the effects of vitamin deficiency on embryonic development comes from nutritional studies of farm and laboratory animals. Although the tendency to draw morals for the human from animal experimentation has often been the object of clinical disapproval, it must be remembered that, in the field of nutrition and in a number of aspects of physiology, many observations which are now universally accepted as applying equally to man have never been, and may never be, proved true for the human species. The significance of vitamins in the normal development of other mammals may therefore justifiably be expected to have some counterpart in human development.

Importance of Vitamins to the Survival of the Embryo

The first vitamin whose importance to the survival of the embryo was definitely established was that which has come to be called vitamin E (Evans and Bishop, 1922). In vitamin-E deficiency the placental blood vessels degenerate; the embryo, thus deprived of oxygen, dies and is resorbed into the tissues of its mother. The paper in which this discovery was first announced was entitled "On the Existence of a Hitherto Unrecognized Dietary Factor Essential for Reproduction." Since then this concept of a direct influence of vitamin E on reproduction has been stressed so often that this vitamin has at times been regarded somewhat naively as a special protector of the developing foetus, standing in a relationship not shared by the other vitamins. Yet a severe degree of maternal vitamin-A deficiency will also cause death of the foetus *in utero* (Warkany and Nelson,

1942), and maternal hypovitaminosis-K gives rise to haemorrhage between the placenta and the uterine wall, with consequent death and abortion of the young (Moore *et al.*, 1942). In fact, all the vitamins are as essential for reproduction as they are for survival. The effect of a mixed or single vitamin deficiency on the survival of the young is as follows. With gross deficiency the health of the female is generally so poor that she is unable to conceive. With less severe deficiency she may conceive and then abort the foetus in the early months of pregnancy. With milder degrees of deficiency she will continue to carry the young throughout pregnancy, but they are born dead or prematurely, and often with some deformity. Only if the diet is adequate will all the young be born healthy and thrive.

Influence of Deficiencies of Individual Vitamins on Development of the Embryo

Vitamin A

The outstanding importance of vitamin-A deficiency in the production of malformations is underlined by the fact that acceptance of the idea that environmental as well as genetic factors can cause congenital deformities in mammals is primarily due to the results of experiments on maternal hypovitaminosis-A (see Warkany, 1947, 1953).

Hale (1935) obtained pigs with absent eyeballs in litters born to sows fed on a diet deficient in vitamin A. By subsequently breeding normal young from the sows and finding no evidence of the deformity in other progeny of the boar, he was able to rule out the possibility that a genetic factor was at work. In this way Hale showed for the first time that a maternal dietary deficiency could cause the birth of deformed young.

This effect of vitamin-A deficiency was soon amply confirmed by the experiments of other workers, notably by Warkany and his collaborators of the Children's Hospital Research Foundation and the University of Cincinnati.

In experimental hypovitaminosis-A virtually all the congenital defects which occur in man have been faithfully reproduced. Congenital defects of the heart and brain, diaphragmatic herniae, horseshoe kidneys, and cleft palates have all been encountered in the young of dams subjected to experimental vitamin-A deficiency. It has recently been shown that hydrocephalus, a congenital defect which when it occurs in man is often explained on a hereditary basis, occurs also in the young of rabbits subjected to experimental vitamin-A deficiency (Figs. 1 and 2) (Millen *et al.*, 1953, 1954). To study this condition a colony of female rabbits was set up at the Department of Anatomy, Cambridge, with the support of the Nuffield Foundation, in 1953. In the past two years 180 hydrocephalic young, 70% of all young born in the colony, have been obtained from 50 does with experimental hypovitaminosis-A. If the mother is given a deficient diet for 20 weeks before mating, the incidence of hydrocephalus in the litters is almost 100% (Millen and

FIG. 1.—Rabbit with hydrocephalus born to mother on a diet deficient in vitamin A.

FIG. 2.—Brain of hydrocephalic rabbit showing gross dilatation of ventricular cavities.

Woollam, 1955). Until this technique for producing hydrocephalus was discovered, the only available method of providing animals with hydrocephalus, for the study of possible therapeutic measures for the condition, was by tedious surgical intervention of doubtful validity. It is to be expected that, in the future, experimental vitamin deficiency will be used increasingly as a tool in the provision of experimental animals for research into the treatment of human congenital deformities. In this respect the ability to reproduce congenital disease of the heart might become of particular interest to the experimental surgeon.

Members of the Vitamin-B₆ Group

Riboflavine (Vitamin B₂).—It has been found that riboflavine deficiency has a marked effect on the development of the skeleton of both birds and mammals. The eggs of a hen on a riboflavine-deficient diet have a low fertility; such chicks as do hatch are poorly developed, with shortened limbs, liver changes, and anaemia (Romanoff and Bauernfeind, 1942). Most of our knowledge of the effects of this deficiency in mammals comes from the work on rats of Warkany and his collaborators (see Warkany and Nelson, 1941). When a rat is subjected to experimental riboflavine deficiency about one-third of her young show one or more of the following deformities: shortening of the limbs, fusion of the fingers and toes, and cleft palate. Examination of the affected bones shows that the process of ossification is arrested at the stage of chondrification, so that the bones remain in a primitive stage of development. It is evident that there is a large requirement for riboflavine in the later stages of bone development.

Pantothenic Acid.—If pantothenic acid is excluded from the maternal dietary two types of deformity are encountered in the young. In the first, the brain lies exposed on the surface of the head through failure of its coverings to develop. In the second, there is failure of the eyeball to appear (Lefébvre-Boisselot, 1951). The first condition bears a resemblance to the pathological findings in *anencephaly*, a deformity quite commonly observed in stillborn children.

Pteroylglutamic Acid.—In recent years many experiments have been performed in which deficiency of pteroylglutamic (folic) acid has been produced, either by the use of a deficient diet or by introducing a pteroylglutamic acid antagonist (*x*-methylpteroylglutamic acid) into a diet already deficient in the vitamin (Nelson *et al.*, 1952). By these means animals have been produced with deformities, including cleft palate, syndactylism, and ectocardia, all of which are encountered as congenital malformations in man.

Vitamin E

The importance of vitamin E to the survival of the foetus has been noted above. There is little information available on whether minor degrees of deficiency of the vitamin have any effect in producing deformities. It has been shown, however, that "stiff-lamb disease," a muscular disorder of newborn lambs, is cured by giving an adequate supply of vitamin E to the mothers (Willman *et al.*, 1931).

Vitamins C and D

There remain two vitamins which are of the greatest importance to life at all ages—vitamins C and D. So far as is known, a deficiency of either of these vitamins does not produce congenital deformities, but acts at a later stage, producing lesions comparable to those encountered in the adult.

Vitamin C.—A foetus suffering from ascorbic-acid deficiency shows lesions of the mouth and haemorrhages under the skin remarkably similar to the condition of scurvy seen in the adult suffering from hypovitaminosis-C (see Reyher *et al.*, 1928).

Vitamin D.—Warkany (1943), by feeding rats on a diet deficient in vitamin D and depriving them of ultra-violet light, obtained young with deformities of the ribs and long bones of the limbs. Both in the sites affected and in the appearance of the lesions these deformities exactly resembled the stigmata of rickets as seen in the growing child. In parts of China where the diet is particularly poor in vitamin D and calcium, the birth of rickety children is frequently observed, and the addition of adequate quantities of vitamin D to the maternal diet has prevented the occurrence of the deformities (Liu *et al.*, 1941).

Mechanism by which Vitamin Deficiencies Affect Embryonic Development

Some authorities still dispute whether a vitamin deficiency produces malformations of the foetus through a primary action on the tissues of the foetus or indirectly by interfering with either the maternal tissues or the placenta. It would seem likely on several grounds that the effect is a direct one on the embryo. It might be argued from the analogy of *x*-radiation, which directly affects the foetus and produces similar deformities, that vitamin deficiencies directly affect the development of the foetus. This view is also supported by the fact that comparable malformations are found in chicks hatched from eggs laid by vitamin-deficient hens.

A deficiency of vitamins results in a disturbance of the metabolic processes of the cell. In the case of some vitamins we know how this is brought about. These vitamins are known to form a part of enzymes which control the metabolic activity of cells. Thus purines and pyrimidines are synthesized with the aid of pteroylglutamic acid. They, as well as riboflavine, are incorporated in enzymes directly concerned with the biochemical processes which play an important part in normal development. Riboflavine is a constituent of the yellow respiratory enzyme, and pantothenic acid of coenzyme A. In recent years the effects of deficiency of various vitamins have been studied at the biochemical level. In riboflavine deficiency there has been found a diminution of succinioxidase in the liver, and of amine, cytochrome, xanthine, and D-amino-acid oxidases (Lévy, 1953). Since it is known that different organs of the body have a different enzymatic constitution, it is easy to see how interference with the function of an enzyme may produce a serious defect of development in one organ and leave another unaffected.

This explanation of the mechanism of vitamin deficiency in abnormal development does not answer every problem. A difficulty is caused by the malformations of the organs of reproduction. The development of these organs is known to be determined by the action of sex hormones. Therefore, if in a vitamin deficiency maldevelopment of these organs occurs, it could be either directly or through the alteration of a normal line of development determined by the

hormones secreted by the testis or ovary. This suggests that to seek an explanation for some errors of development we may have to implicate the structures which control normal development—for example, the pituitary gland—and postulate an enzymatic dysfunction in these structures rather than in the organs whose development they control.

Conclusions

The modern view of the vitamins is that they are complex chemical substances, essential to life by virtue of their role in the biochemical processes of the cell. Vitamins have to be obtained from the diet because of the inability of the body to synthesize them. The increased demand by the pregnant woman for vitamins reflects the need of the embryo to build up a store of these substances for its own biochemical processes. It is evident beyond doubt from animal experiments that if the minimum requirement is not met the embryo will either die or be born congenitally deformed.

What validity these animal experiments have for conditions in the human is as yet impossible to say. It must be noted, however, that if human conditions do correspond to those in the animal the administration of vitamins during pregnancy is of little avail to the embryo. Minor degrees of experimental vitamin deficiencies exert their effect in producing malformations during the early months of pregnancy, at a time when even the existence of pregnancy may not be evident to the woman. In obstetric practice vitamins are commonly prescribed in the middle and late months of pregnancy. The results of the animal experimentation described above suggest that the only way in which the nutrition of the embryo can be safeguarded is by attention being directed towards the diet of women throughout their lives, and especially of girls in the later stages of adolescence. Only by reorientating our attitude in this way can we ensure that the members of the next generation develop in bodies which provide an adequate supply of essential foodstuffs from the very outset of pregnancy.

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The Trustees of the Margaret de Sousa Deiro Fund wish to draw the attention of medical practitioners to the scope of this Fund. It exists to provide for the treatment and relief of women who normally support themselves by their own exertions but are temporarily incapacitated by pulmonary tuberculosis. There are grants to cover the cost of treatment, when this cannot be carried out in suitable conditions under the National Health Service, and grants towards convalescent holidays following institutional treatment. In approved cases the Trustees also give financial assistance for rehabilitation, if part-time work would mean an inadequate living wage. Further details are obtainable from the Trustees, 1, New Court, Carey Street, Lincoln's Inn, London, W.C.2.

SUSPENDER DERMATITIS AND NICKEL SENSITIVITY

BY

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Dermatitis and eczema of various patterns comprise the largest and most difficult part of dermatology for the practitioner and specialist. A certain proportion of these cases appear to be due to external contact with substances which behave as allergens. These cases assume especial importance, because if the cause is identified and further contact avoided the patient may have no further trouble.

Contact dermatitis from allergy to nickel has been known for a long time, especially in industrial processes, but none of the recent literature reflects the fact that it is now such a frequent occurrence among women apart from industry. Reviews of the subject have been published by Goldman (1933) and Foster and Ball (1935). More recently, Morgan (1953) used a series of 54 cases over a ten-year period to investigate the persistence of allergic contact sensitivity.

Incidence

Allergic contact dermatitis has been studied in a special clinic at St. John's Hospital for Diseases of the Skin over the past three years. At an early stage in this work we became very impressed by the enormous frequency of allergic sensitivity in women, manifest by patches of dermatitis under their suspenders. Unfortunately, we have no earlier records to prove whether the true incidence of this condition has increased or not, but its significance and importance are becoming better recognized. It is now by far the commonest type of sensitivity dermatitis encountered in routine dermatological practice. The results of patch tests in our clinic over the past three years are as follows:

	Total Positives	Nickel Positives
1953	478	131
1954	412	198
1955	420	180

By no means all cases are patch-tested, and we estimate that these figures represent about half the true incidence of nickel sensitivity in women among the 18,000 to 20,000 new patients seen each year at this hospital. It is possible,

FIG. 1.—Schematic drawing to illustrate sites of primary eruption.