NO NATION CAN RISE ABOVE THE LEVEL OF ITS WOMEN

**New thoughts on maternal nutrition
by
Margaret Wynn and Arthur Wynn**

MARGARET AND ARTHUR WYNN

From her early work on family and social policy, to the pioneering studies of the importance of nutrition to mothers and babies in promoting good health, Margaret Wynn is in a great tradition of social reformers. She has worked with her husband, Arthur, since he retired as a senior civil servant: and the two of them have been champions of the health and welfare of mothers and children, in this country and worldwide. Their great book, *Prevention of Handicap and the Health of Women* was published in 1979, and they are still ahead of the nutritional establishment. They recently starred in the Channel 4 series *Eat Up*.

THE CAROLINE WALKER TRUST

The Trust was set up in memory of the food writer and campaigner Caroline Walker, who died in 1988. The Trust's mission is the promotion of public of health by means of good food – a cause which Caroline made important to everybody in this country. The Trust, which relies on charitable donations, exists to further her work through research and publications.

It is a privilege to address this Evening of Celebration of the Caroline Walker Trust. I heard Caroline speak on several occasions. I saw her on television, and most memorably on the diets of school girls and boys. I think of her not just as a brilliant dietitian and a gifted speaker, but as a politician in the sense that Robert McCarrison, John Boyd Orr, Bill de Gros Clark, and Jack Drummond were politicians of food and nutrition. They presented good food as essential for the health of individuals, of the next generation and of nations. Caroline's legacy is in the purpose of this Trust: "To improve public health by means of good food". In 1984 Caroline and Geoffrey Cannon wrote [1]:

> "The importance of positively good food, above all when preparing for pregnancy, is a message vital to the health of the child as well as the mother."

The President of this Trust made this a general truth when he wrote: "The health of our children is our most precious resource."

Arthur and I have taken as our title a message from a generation not only older than Caroline but older than ourselves. "No nation can rise above the level of its women" are the words of Mrs Leonora Cohen. She was known as "the Tower suffragette," because she smashed the glass of the Crown Jewels' case in the Tower of London with a bar from her own fireplace, wrapped in a piece of paper on which she had written: "Denying the vote is treachery to the working women of Britain". Miss Elspeth Rhys Williams (whose mother headed the project of the National Birthday Trust to feed pregnant women in the Depressed Areas in the 1930s), visited Mrs Cohen and told us her views:

> "Every child has a right to be well-born; a farmer looks after his stock better than we look after human beings. The suffragettes were fighting for motherhood and no nation can rise above the level of its women."

In 1978 we asked the matron of the Home in which Mrs. Cohen was living to ask her permission to quote these words. She was pleased to say yes. She died a few weeks later at the age of 105.

The long arm of maternal nutrition

The health and education of women affects the health and expectation of life of the next generation. Many disorders and disabilities of adults are already present in childhood. This is true of ischaemic heart disease, a major cause of death in middle age [2]; and it is true of brain disorders, the most costly of all disorders affecting adults, but already present in one child in eight according to American data [3]. Evidence given to the US Congress showed that most of these disorders are already present at birth [4]. For every child with a recognised brain disorder or heart defect there are, of course, others with subclinical, undiagnosed minor impairments.

What part does faulty maternal nutrition play in the origin of these human disorders and disabilities of early origin? There is one obvious clue, that maternal nutrition may be involved in the association of maldevelopment and a slow-down in growth some time before birth. A former co-ordinator of the WHO Maternal and Child Health Programme summarised [5]:

"Low birthweight is one of the most serious public health problems in the world today. It is estimated that more than 20 million low birthweight babies are born every year... they account for a high proportion of infant mortality. If they survive they suffer from higher rates of childhood illness and more or less permanent and severe disabling conditions such as mental retardation, behavioural disorders, cerebral palsy and impairment of vision and deafness."

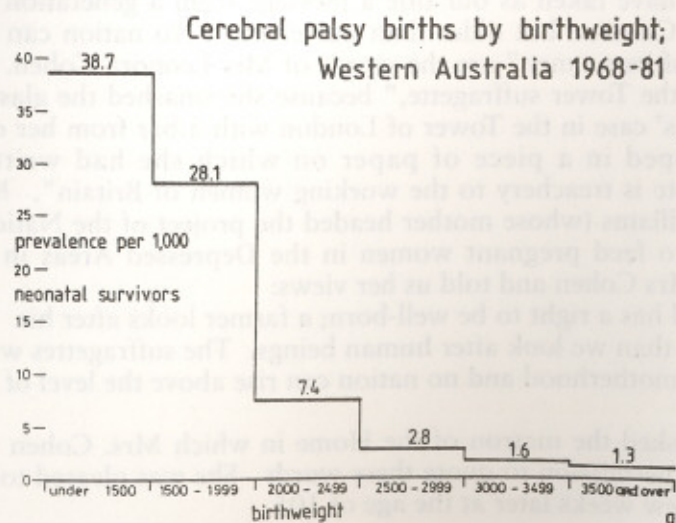Cerebral palsy births by birthweight; Western Australia 1968-81

Figure 1. Reference 6

Figure 1 shows for example the association between the risk of cerebral palsy and birthweight using Australian data [6]. Maternal nutrition and infant growth are connected – although the character of the connection is not obvious. Are they cause and effect, or do both spring from a common cause? An association has been shown between a poor habitual maternal diet and low birthweight, but when does the poor diet have its greatest effect on the growth and development of the next generation? Does defective maternal nutrition only affect embryo and fetus – or can it also injure the genome and the human genetic heritage? Well-fed women have very few low birthweight babies. But what do we mean by well-fed and ill-fed in this context, given that there are many essential nutrients with complicated connections with human growth? These are some of the questions we shall address.

The story of iodine deficiency and birth defects

The first interim answers to some of the more important of our questions were provided historically by the consequences of a dietary deficiency of the single element iodine.

During the early years of the first world war, over 1 million piglets in the State of Montana were dying every year within 36 hours of birth or were born dead [7]. The piglets were unusually small, hairless and had malformed hearts and many other defects. Their thyroid glands were greatly enlarged and contained only very low concentrations of iodine. The University of Montana undertook successful controlled trials of iodine supplementation of the sows on one and then on five ranches, and overcame the epidemic.

In Vancouver in the 1920s there was much concern among the settlers at the high stillbirth and neonatal (or new-born) death rates of human infants. Iodine deficiency began to look like the culprit when it was discovered that the stillbirth rate of Indians living on the coast of British Columbia, who had very limited medical services, was only 12.6 per 1000, compared with 27.3 per 1000 for the settlers for the years 1923 to 1929 [8]. There was much goitre among the settlers (including 8 per cent among the children), but no goitre among the coastal Indians – who ate fish and seafoods, which may contain 100 times as much iodine per gram as food originating from the land, such as grains and vegetables. Supplementation of pregnant women with iodine was claimed to be partially successful in reducing casualties, but only the general introduction of iodised salt, which took place on a world scale in the 1920s, caused the problem to disappear [9].

Every continent has its history associating fertility and satisfactory

human reproduction with maternal consumption of sea foods. Chinese texts go back to 1600 BC and Indian texts to 1400 BC and Marco Polo referred to the eastern traditions in 1271 AD [10]. Sir Robert McCarrison published 5 books on iodine and the thyroid gland between 1913 and 1932, which were mostly based on his experiences in India [11 to 15].

Research in recent years has confirmed that iodine deficiency does indeed do its worst damage very early in pregnancy, and earlier still, before conception. Thus research by Peter Pharoah, now professor in Liverpool, and colleagues in the Highlands of New Guinea, showed that iodised oil was effective in the treatment of endemic cretinism and its multiple neurological defects including deaf-mutism, mental retardation, squint and spastic diplegia (paralysis of two sides of the body) [16]. However, to be effective, iodised oil had to be given before conception. Giving it after diagnosis of pregnancy was too late. This important conclusion was in line with earlier animal experiments in the Netherlands using rats, which showed that thyroid hormone deficiency beginning 7 to 43 days *before* mating produced a great range of congenital defects in offspring, but thyroid deficiency beginning as early as 2 days *after* mating had no such effects [17]. The story of iodine shows that human reproduction is susceptible, around the time of and before conception, to a deficiency of a single nutrient.

Iodine deficiency does, of course, have pathological consequences at all ages. The mothers of afflicted babies generally have goitre. Fetal brain development is retarded by deficiency in the womb, but the most serious consequences are those that originate before or around conception [18]. The story of iodine also showed that a series of disorders of the brain, such as mental retardation and spastic diplegia, could have their origin very early in pregnancy even before conception. Pharoah and colleagues concluded their 1971 paper in the Lancet [16].

> "If the role played by iodine in the aetiology of the deaf-mute,
> squinting, mental deficiency, congenital diplegia of endemic cretinism
> can be determined, this may indicate further lines of investigation in
> the aetiology of other congenital spastic diplegias."

This extensive medical literature and history about iodine prompts a series of hypotheses about maternal nutrition of wider significance. Why only iodine? That disorders such as goitre and hypothyroidism in the mother are associated with stillbirth and many serious disorders of the infants prompts the question: what other maternal nutritional deficiencies and maternal disorders are associated with an unsatisfactory pregnancy outcome? The iodine experience has indeed pointed towards new lines of investigation.

Depressed hormone levels and neurological disorders

Iodine is an essential constituent of thyroid hormones and there is little evidence that it has any other role. The neurological disorders, such as spastic diplegia, are a consequence of depressed levels of thyroid hormones; and these depressed levels have repercussions on the levels of other hormones also concerned with reproduction. In particular a depression in thyroid hormone levels causes a depression in the levels of the two sex hormones oestradiol and progesterone [19-21].

Because iodine deficiency apparently produces all its consequences through thyroid hormones and the endocrine system, we may conclude that depressed hormone levels are probably responsible for these consequences – which include low birthweight, maldevelopment of the nervous system including spastic diplegia and mental retardation. The theme of this paper therefore moves to a discussion of hormones with such questions as: What nutrient deficiencies other than iodine depress the levels of the sex hormones? But first let us conclude the discussion of iodine with a quotation and comment on iodine in the British diet from Pharoah and colleagues in 1979 [22]:

> "Endemic cretinism is now a disease of the third world only. Whilst
> its prevention is a laudable and feasible goal the likelihood that the
> motor and possibly mental performance of whole populations may
> be increased by iodine supplementation is of great medical and social
> importance."

The Dietary and Nutritional Survey of British Adults (1990) published by the Office of Population Censuses and Surveys found one woman in forty aged 16 to 24 with a daily iodine intake below 51 mcg/day and aged 25 to 34 below 53 mcg/day [23]. This is only about a third of the median iodine intake of 161 mcg/day. The COMA report on dietary reference values recommends 140 mcg/day and quotes sources reporting a risk of goitre below 70 mcg/day [24]. There appears indeed to be a minority of women in Britain today with iodine intakes low enough to affect the development of the next generation of children (The Chinese say, "these ladies should sprinkle some dried seaweed into their wine"). However iodine deficiency of diet is not the most important cause of hormonal depression or even hypothyroidism in Britain today.

Slimming and reproductive hormone levels

Martin Pirke and colleagues at the Max Planck Institute of Psychiatry in Munich have published a long series of studies showing the interaction of nutrition with the levels of these hormones [25]. Figure 2 shows the rapid

Decline of oestradiol (E2) levels in blood following
dieting, averages for 6 women 24 measurements per woman
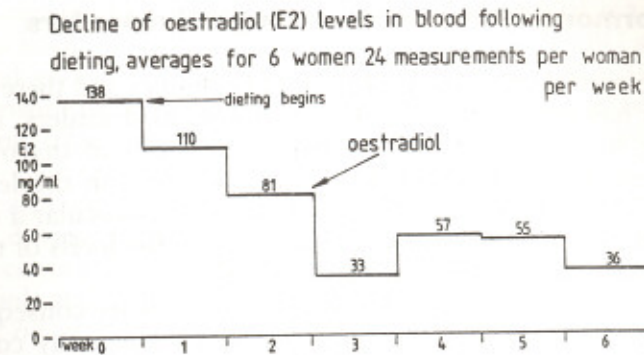per week

Figure 2. Reference 26

decline in oestradiol levels following change from a normal to a slimming diet. Figure 3 shows the similar decline in levels of progesterone [26]. Both figures are the result of measurements on 6 healthy young women who volunteered to follow a slimming diet of about 1,000 kcal/day for 6 weeks. Such declines in sex hormone levels result in complete infertility, as does a similar decline in thyroid hormone level. Maldevelopment and also miscarriage happen at marginal levels of depression of oestradiol and progesterone – when levels are high enough not to prevent ovulation and fertilisation, but too low to support a healthy pregnancy. In other words, slimming alone can stop ovulation and cause temporary infertility by depressing sex hormone levels; and at a marginal level of malnutrition, when diet is only just adequate for fertility, it can cause low birthweight.
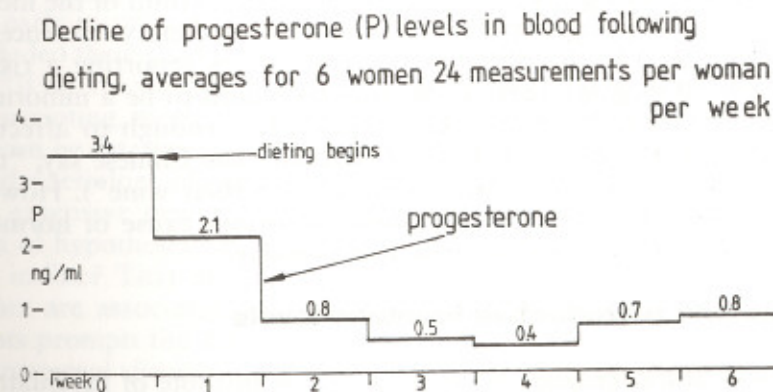
Decline of progesterone (P) levels in blood following
dieting, averages for 6 women 24 measurements per woman
per week

Figure 3. Reference 26

The menstrual cycle as a marker of hormone status

Different diets and individual nutrients have different effects on hormone profiles, and they merit further discussion, but there is an important practical question. Is there any way a woman can tell whether her hormone levels are satisfactory? We quote from a report of the US National Research Council [27]:

"Menstrual cycles constitute the most accessible and non-invasive biological markers of female reproductive functions in humans."

D.T. Baird, in a chapter on amenorrhoea (missed periods) in a well-known 3 volume treatise on endocrinology says [28]:

"A careful dietary history and weight record should be sought in all women who complain of amenorrhoea. The most common clinical feature of women who present with this symptom is a history of weight loss, usually caused by voluntary dietary restriction."

Hormone levels can, however, also be disturbed by a range of toxic substances, and some drugs (such as tranquillisers and analgesics). The marginal levels of reproductive hormones that are associated with an increased risk of slow development in babies are indicated by an increased length of cycle. Measurements of more than a quarter of a million menstrual cycles by Treloar in the U.S.A. found a median of 28 days for very young women, falling to about 26 days at age 40 to 45 [29]. 26 to 28 days is a healthy length of cycle and cycles of this length are evidence that hormone levels are not being depressed by a less than satisfactory diet. What then does a long cycle indicate?

Maternal nutrition and the length of the follicular phase

The time-table of the reproductive cycle in women is shown diagrammatically in Figure 4. The first stage of the cycle from the beginning of menstruation until ovulation is called the follicular phase. In women in good health it lasts about 14 days. A slow-down in follicular development, and increase in length of the follicular phase, may be a consequence of poor maternal nutrition, but also of toxic substances and some drugs. Research sponsored by the French Medical Research Council (INSERM) has shown that an increased length of the follicular phase of the cycle, and of the whole cycle, are both markers of an increased risk of babies born with malformations and of retarded fetal growth [30]. French experiments showing the longer follicular phase associated with malformations at birth are shown in Figure 5 [31]. The French authors acknowledged their indebtedness to quite extensive animal research in the U.S.A. and Japan, which showed that not only congenital malformations, but genetic
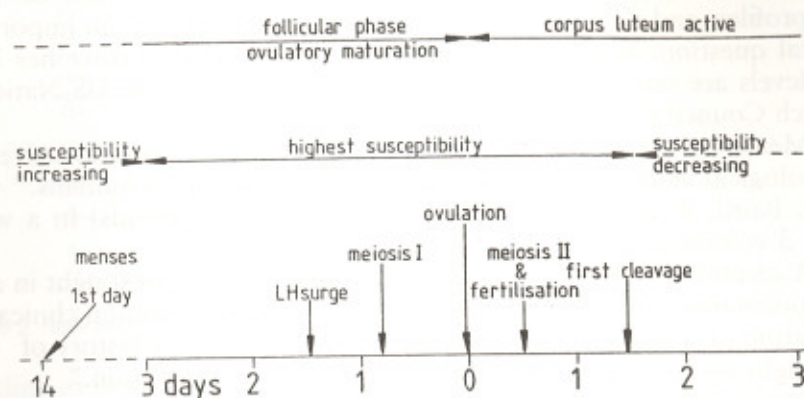
Women's susceptibility around ovulation

Figure 4. Reference 32

damage could be produced by slow follicular development and delayed ovulation. There is a summary in our book on preconception care [32].

Maternal nutrition and the growth of oocyte and follicle

When does damage happen? The human oocyte, that eventually grows to become the fertilised ovum and the baby, wakes up from a deep sleep about 65 days before ovulation [33]. Before its awakening, the oocyte is very resistant to most external influences. However, about 14 days before ovulation, that is at the beginning of the follicular phase illustrated in Figure 4, the endocrine system begins to respond to messages from the developing oocyte. Poor maternal nutrition results in a less than satisfactory response, and in hormone levels inadequate to stimulate growth of both the oocyte and the follicle. The follicular phase of the menstrual cycle – from the beginning of menses until ovulation – is highly sensitive to maternal nutrition. In taking a new look at maternal nutrition, it must be stressed that the rapidity of response to changes in diet only appears to have been appreciated quite recently following research both on primates [34] and on women volunteers [35]. It is during the 14 days before conception that it is most important for diet to be adequate and regular, with no missed meals. Both long-term, habitual diet and short-term, contemporary diet affect follicular development.

A healthy follicle may increase in mass by more than 2,000 times during the first 14 days of the menstrual cycle before ovulation, as shown in

Figure 6 [36]. The follicle before extruding the ovum may be 25mm (1 inch) in diameter. The ovum at ovulation weighs about 300 times as much as the oocyte before it woke from its long sleep: it reaches a diameter of nearly a millimetre at ovulation [37]. It is the normal rapid growth of the follicle and of the oocyte it contains, during these 14 days of the follicular stage which is disturbed and prolonged by poor nutrition mediated by the endocrine system. A review paper in a number of Mutation Research devoted to "Female germ cells: biology and genetic risk" writes [38]:

> "The quality of gametes and embryos is determined by the hormonal modification of the genetic program during intra-ovarian development."

Recent research on in vitro fertilisation has also shown that oestradiol, a growth promoter, and other hormone concentrations have to reach a critical level during the follicular phase for the ovum to be viable [39-41].

Necessary luggage for the developing ovum

It is not the genes and chromosomes that increase in mass during follicular development but the rest of the oocyte. During follicular development, it begins to transcribe and translate genes – mainly into proteins that are essential later, during the initial stages of development of the embryo. The ovum begins its long journey at ovulation with what may be described as necessary luggage weighing some hundreds of times as much as the actual genome. If maternal nutrition is inadequate, the luggage may be inadequate for the first stages of the journey. Molecular analysis today has

Risk of congenital malformations by length of the follicular phase prior to the conception 916 couples France 1979-82
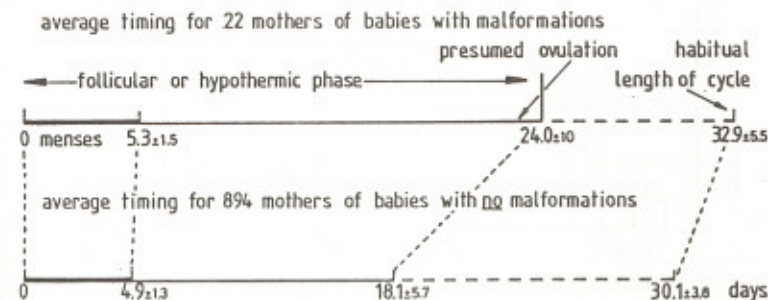
Figure 5. Reference 31

Growth of the follicle

day 1 of menses   day 14
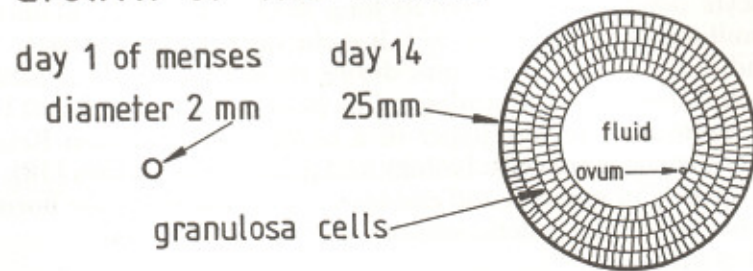
diameter 2 mm   25mm

fluid

ovum

granulosa cells

Figure 6. Reference 32

made it possible to track particular proteins through the stages from follicle to implanted embryo [42]. These proteins can be inadequate or damaged already at the follicular stage: if so they prejudice all subsequent development of the particular ovum. A slow-down of follicular development, and a delay in ovulation, are both therefore markers of inadequate or defective luggage.

Growth of the follicle ceases at ovulation when the oocyte becomes the ovum and is extruded. The follicle then turns into a new endocrine organ, the corpus luteum, which produces progesterone to support the ovum. Poor maternal nutrition can result in a corpus luteum that is too small or defective, and that will lead to an inadequate supply of progesterone;

Protein before pregnancy affects early embryo

48 hours after mating

diet before mating
— standard protein 27%
- - - low protein 8%

number of ova

1 cell: 14, 64
2 cell: 15, 32
4-8 cell: 45, 25
12 or more cells: 92, 4

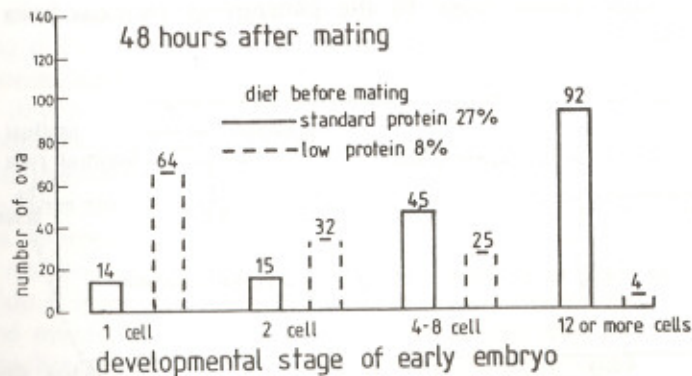developmental stage of early embryo

Figure 7. Reference 44

resulting in failure of implantation or early miscarriage [43]. Maternal nutrition thus affects both the quality of the ovum produced at ovulation and the subsequent hormonal environment of the early embryo. In short, a mother's nutrition affects the next generation from its early development even before conception.

Damage to the genome by defective maternal nutrition is yet another way in which the embryo may be affected already before ovulation. But we'll defer discussion of damage to the genome until we've said a little more about some components of diet and some ways of cooking.

Protein before pregnancy and percentage abnormal ova

low protein 15% — 72.1, 72.2

30 days on diet before mating

high protein 35% — 51.9, 49.5, 40.9, 26.4

average abnormal ova per mouse dam %

standard protein 25% — 1.3, 4.4, 6.0, 6.5

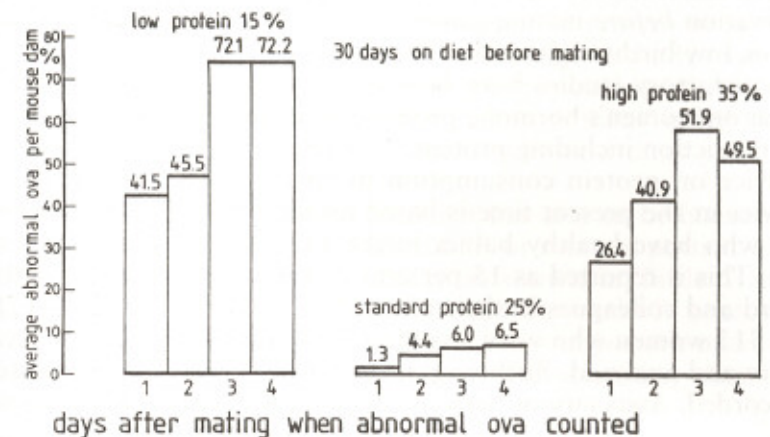days after mating when abnormal ova counted

Figure 8. Reference 45

Protein in maternal diet and the outcome of pregnancy

Animal experimentation has shown that there are optimal protein intakes during the period before mating, with variations between animal species. In these experiments, protein consumption below optimum had several effects: it depressed levels of the two sex hormones oestradiol and progesterone; it inhibited or delayed ovulation; it increased the percentage of defective ova; and it increased the percentage of ova with chromosomal aberrations or damage to the genome. A mother's low protein intake before mating causes an increased length of time to first cleavage as shown in Figure 7 from experiments on mice [44]. A low protein diet was given to one group of mice 14 days before mating; `another group had a

standard diet. As Figure 7 shows, 48 hours later most of the embryos of control mice fed a standard diet had progressed to 12 cells already – while the embryos of protein-starved mice had mostly not divided at all, or were still in the 2-cell or 4 to 8-cell stage. There were fast and slow lanes of development, with embryos of mice fed the standard diet in the fast lane. It's worth noting that an *increase* in protein in maternal diet, to levels above the optimum in mice, also increases the percentage of defective ova as shown in Figure 8 [45].

As to timing, pregnancy outcome is most affected by protein status during the period immediately preceding mating – particularly in the larger animals with substantial protein stores. Thus piglets are little affected by protein starvation of the sow after mating during pregnancy; but protein starvation *before* mating causes the usual effects: reduced or delayed ovulation, low birthweight and stillbirth [46].

No satisfactory studies have been found of the effect of protein consumption on women's hormone profiles, only indeed the effects of general dietary restriction including protein. This research should be done to support advice on protein consumption in anticipation of pregnancy. The best advice at the present time is based on the protein now consumed by women who have healthy babies in the best birthweight range (3,500-4,500g). This is reported as 15 per cent of calories as protein by Michael Crawford and colleagues in their research in Hackney, London [47]. The diets of 513 women who were less than 3 months pregnant were recorded in a diary and analysed. Birthweight, birth length and head circumference were recorded. Associations between diet and these birth dimensions have

Table 1: Correlates of protein with vitamins and minerals in the diets of 513 London mothers

nutrient	correlation coefficient
sulphur	0.918
phosphorus	0.864
zinc	0.836
pantothenic acid	0.792
potassium	0.741
thiamin B1	0.731
niacin B3	0.718
riboflavin B2	0.700
calcium	0.698
pyridoxine B6	0.649
magnesium	0.646
biotin	0.622
folate	0.547
copper	0.486
iron	0.484

Source: Doyle, W. Personal communication

been published. There were 165 mothers who had babies in the optimum birthweight range 3,500 to 4,500g. The median daily protein intake of 73g by these 165 mothers, or 15 per cent of calories, was only slightly above the median figure for women of all ages of 14.5 per cent recorded by the Dietary and Nutritional Survey of British Adults [23]; it was well above the 51g officially recommended for pregnant women in the UK.

For the mothers of babies below the median birthweight of 3,270g in the Hackney study, there was a highly significant correlation between birthweight, head size and protein consumption towards the end of the first trimester of pregnancy (and assumed to be similar to the habitual diet).

It is not clear from any research what safety margin there may be in the recommendation of 15 per cent of calories as protein in advance of pregnancy, and use of a lower figure seems unwise. In the Hackney study it was found that nearly all the mothers of low birthweight babies not only had low protein intakes, but low intakes of many other nutrients. There was, indeed, a minority of mothers who had diets poor by any standard.

In making practical recommendations it has also to be borne in mind that in the British diet the daily intake of 15 or more important nutrients is highly correlated with protein intake as shown in Table 1 from the Hackney study. It is not possible to reduce protein intake in practice without at the same time reducing the intake of other important nutrients like zinc and thiamin (B1) known to be important for pregnancy outcome.

Lessons from the folic acid story

In July 1991, the results of the Medical Research Council (MRC) Vitamin Study, of folic acid supplementation in preventing the repetition of neural tube defects such as spina bifida, were published and received much publicity [48]. The trial showed that folic acid supplements taken before conception had a 72 per cent protective effect against a repetition of neural tube malformations. A committee appointed by Dr Kenneth Calman, Chief Medical Officer of the Department of Health, recommended that all women who are planning a pregnancy should be advised to purchase and take 400 mcg of folic acid daily and doctors should increase this by prescription to 4 mg when there was a history of neural tube defects [49]. This MRC study initiated an important advance in preventive medicine.

What may be learnt from this advance? Folic acid deficiency has been known for more than 30 years to be mutagenic (that is, to damage the genome or genetic material of an organism) [32]. This is discussed further below, but the story of folic acid by itself should increase our respect for

all things mutagenic – particularly around the time of conception, and most especially before conception.

More and more evidence has pointed to the importance of a normal hormonal profile through maturation of the oocyte and afterwards, for a healthy baby. Folic acid deficiency was reported to depress the levels of oestradiol and progesterone in Rhesus monkeys in 1976 [50]. The folic acid story further emphasises the importance of understanding all those variations in diet that modify hormone profiles in dangerous directions – not forgetting the synergistic contribution of some drugs and toxins.

Folic acid deficiency has also been shown to slow down the replication of the granulosa cells, the principal cells within the ovarian follicle, and thus to slow-down the growth of the follicle and delay ovulation [51]. The same study confirmed that folic acid deficiency depressed levels of the reproductive hormones oestradiol and progesterone. This further emphasises the importance of the length of the follicular phase and the dangers of delayed ovulation: as markers for slow-down in embryonic growth, and the risk of malformations.

Folic acid deficiency was reported by Marjorie Nelson and colleagues at the University of California to cause rats to be born with malformations in 1949, and by Antoinette Giroud and colleagues at the University of Paris in 1951 [52] [53]. These and later experiments showed that folic acid deficiency caused neural tube defects and also defects of the eyes, digestive tract, lungs, skeleton including club-foot and face including cleft palate. Such experiments establish hypotheses for humans. There are probably more effects to be discovered: it is unlikely that a deficiency like that of folic acid which increases mutation rates only produces neural tube defects.

Mothers, magnesium, and the outcome of pregnancy

Maternal magnesium intake in the Hackney study was more closely related to birthweight than any other nutrient; and the second closest to social class after folic acid [54]. Animal experiments show that magnesium deficiency can cause sterility, low birthweight, congenital malformations, raised maternal blood pressure and damage to the genome. There are studies from a number of countries associating low magnesium intake in pregnant women with miscarriage, low birthweight and raised maternal blood pressure [55].

Magnesium in association with phosphates is required for the local delivery of all the energy needed for cell replication. It is not therefore surprising that low magnesium concentration in human cells slows down everything that requires energy, including growth of the oocyte, follicle,

embryo and fetus. Lucille Hurley and colleagues reported that magnesium deficiency is mutagenic in 1975 [56].

Hormone receptors require magnesium. The binding of the reproductive hormones, oestradiol and progesterone, to target tissues, can be varied in the laboratory over a range of 10 to 1 simply by varying magnesium concentrations [57]. This upsets the idea that satisfactory hormone levels are all that is necessary for healthy reproduction. In order to be effective the hormones have to have magnesium. In fact, to connect them to their targets, they also need other divalent metals for special purposes including calcium, manganese and zinc.

There is a surprising spread in intakes of magnesium in British diets. In the Hackney study intakes varied from 86 to 588 mg/day. The British Adult survey reported 5 per cent of women outside the range 99 to 413 mg/day. COMA's recommended intake is 270 mg/day. There is a minority of women in Britain whose diets are too low in magnesium: and significantly, mothers of low birthweight babies belong to this minority of women with low daily intakes of magnesium.

Maternal zinc consumption and the outcome of pregnancy

There are many studies associating maternal zinc deficiency in mothers whose babies have low birthweight or are born with malformations, and there are more animal studies connecting zinc deficiency with maldevelopment than for any other single nutrient. Lucille Hurley of the University of California published a long review in 1981 [58]. Another review was published in 1993, more specifically on the effects of zinc deficiency on development of the brain and nervous system [59]. Maternal zinc intake was highly correlated with birthweight and head circumference in the Hackney study [47].

Zinc is an essential component of the DNA of the genome and the RNA of the ovular luggage. Thus what are called 'zinc-fingers' are necessary for binding the reproductive steroid hormones, oestradiol and progesterone, and the thyroid hormones, to receptors on the DNA of the genome [60] [61]. These are the particular hormones that have access to the DNA of the genome and stimulate the transcription of the information essential for reproduction carried by the genome. Most hormones only go as far as receptors on the membranes of the cell surfaces. The receptors for the steroid and thyroid hormones use arrangements of zinc-finger motifs to attract and hold the hormones. Large repertoires of DNA sequences can be recognised by arrangement of the receptors with their zinc fingers. Lucille Hurley and colleagues reported that zinc deficiency is mutagenic in 1975 [56].

It is a particular characteristic of zinc that body stores cannot be used at short notice so that blood concentrations go up and down with the diet. Zinc concentration may decline by half in 24 hours on temporary transfer to a low zinc diet [62]. Susceptibility to zinc deficiency in the short term is a good reason for regularity of meals during the period before conception and during early pregnancy.

A review in the journal Teratology in 1992 emphasised that maternal zinc intake offers some protection: it is a modulator of the developmental toxicity of environmental poisons, drugs and some diseases such as diabetes [63]. In practice maldevelopment and damage to the genome is often a consequence of a number of different factors including toxic substances and nutrient deficiencies. The conclusion from the review was that zinc deficiency may often be one of these contributing factors.

The Dietary Survey of British Adults showed a substantial spread in young women's zinc intake, with 2.5 per cent of women in the 25-34 age bracket with intakes below 3.4 mg/day. The mothers of babies in the optimum birthweight bracket had a median intake of 10 mg/day, and 10 mg/day is recommended below for women planning pregnancy. Zinc is one of the nutrients lost in producing white flour products. There is a minority of women with very low zinc intakes.

A new chapter: maternal nutrition and the human genome

Our examples so far of deficiencies in maternal nutrition have all been described as "mutagenic". The word "mutation" was first used in a biological sense in the U.S.A. by W.B. Scott in the 1890s, and has had many shades of meaning. The word was defined in 1978 by the European Environmental Mutagen Society as, "an alteration in the genetic apparatus of an organism" [64]. It is the genetic apparatus – that is, the genome – in sperm and ova that carries inheritance from parents to children. This European society is part of the world organisation, International Commission for Protection against Environmental Mutagens and Carcinogens, or ICPEMC, referred to further below. Most mutations are harmful. The ICPEMC summarised in 1983 [65]:

> "In man mutation must be considered essentially harmful. The harmfulness of mutation can be seen from the fact that a variety of diseases depends on repeated mutation for their continued presence in the population."

Mutagens may change, damage, delete or move genes. Whole chromosomes may be moved or broken. Many toxic substances are mutagenic, and more particularly during the follicular phase in the female and spermatogenesis in the male. Faulty nutrition can also be mutagenic. Mutation

Research, the leading journal in this subject, had a special number on mutations in female germ cells in its 296th volume in 1992 [66], and a special number on male germ cells in its 229th volume in 1990 [67].

Mutations can be environmental in origin in one generation, but genetic in this generation's children – upsetting the old belief that human disorders are *either* hereditary *or* environmental in origin. They may be environmental in parents and inherited by children. There are one-generation genetic diseases like Down's syndrome, which is always inherited by children but very rarely passed on by sufferers, and is generally acquired from parents who were not sufferers [68].

Are mutations an important cause of human disorders? Most research on mutation is financed by cancer research funds on the assumption that reducing mutation rates will reduce the risk of cancer, but amongst the studies published are many describing mutation in germ cells. There is an ever-increasing list of syndromes originating in mutation in germ cells. These include major disorders of the brain and nervous system including Down's syndrome, fragile X syndrome and epilepsy. All three are at least partly a consequence of defects in the genome of fairly recent origin [65]. There are also disorders of other body systems, including heart disease and diabetes, where there is evidence of a partly mutational origin. Poor maternal nutrition is not only a cause of mutation but increases the risk from other causes.

What are the causes of mutation?

That mutations happened was well-established in the last century, but mutations were regarded for many years as rare events. The expert in the Encyclopaedia Britannica as late as the 14th edition, 1929, attributed mutations, "probably to the action of certain radiations pervading the environment". Since about 1960, when environmental mutagen societies were established in most leading countries, there has been an increase every year in the recognised causes of mutation. These causes include viruses, some drugs, many chemicals, some heavy metals like lead, some errors in human metabolism and faulty nutrition.

It was known in the last century that pernicious anaemia seriously damages the genome, even breaking up the chromosomes into fragments. The discovery that a deficiency of either folic acid or cobalamin could cause pernicious anaemia led quickly to the conclusion that these nutrient deficiencies are mutagenic. This was confirmed in a long series of papers from several countries in the 1960s [32]. This was the beginning of the new chapter on the whole subject of maternal nutrition. The importance of this new chapter became apparent when it was shown that more than

Table 2: Pre-conception diet and miscarriage: Yorkshire 1984

	miscarriage	livebirths	births > 3500g
N	9	213	98
kilocalories	1959	2255	2318***
fats g	96	112	114**
zinc mg	9.3	11.8**	12.1**
retinol mcg	1164	2423*	2520*
riboflavin mg	2.2	2.8*	2.9*
niacin mg	18	24*	24**
folate mcg	214	264	276
cobalamin mcg	9	14	15*

Significance of difference from the miscarriage group: * p < 0.05; ** p < 0.01; *** p < 0.001.

Source: Reference 73

half all miscarried embryos had chromosomal aberrations [69]. Some 90 per cent of these miscarried embryos had visible defects. About 20 per cent of reported pregnancies miscarry, to quote American figures [70]. We may infer that mutations of an apparently damaging character in women's germ cells before conception (causing miscarriage) are not rare events; on the contrary, they are all too common. Only the most lethal mutations cause miscarriage, while many others are compatible with survival.

It has been known for many years that early miscarriage as well as an increased risk of congenital malformations followed an abnormally long follicular phase [71]. This provided one link with maternal nutrition – which has been shown experimentally in animals and women to cause delay in ovulation if it was inadequate. Another link came from direct studies of the diets of women who had miscarriages [72]. Table 2 summarises a small study from Yorkshire [73]. It should be added that miscarriages can also be caused by mutations in the sperm of prospective fathers [74].

The discovery of anti-mutagens

Then came a major advance in our understanding of the connection between maternal nutrition and the protection of the genome: the discovery in the early 1980s that many essential nutrients are anti-mutagens [75]. These include some of the B vitamins – for example riboflavin (B2) – vitamins A,C and E, and the minerals zinc and selenium [76]. Some of these anti-mutagens are also harmful or mutagenic in excess, including vitamin A, zinc and selenium. Monounsaturated and polyunsaturated fats are anti-mutagenic with an important role in inactivating mutagens in the digestive tract [77]. Mutation Research in 1992 had a 142 page special issue on the assessment of anti-mutagenicity and anti-carcinogenicity [78].

Yet a further advance in the 1980s was the discovery of a growing number of components of diet that are anti-mutagenic but are not known to be essential nutrients. We have therefore now a new family of nutrients that are desirable, but not classified as essential. These include carotene; the catechins in tea; and chlorophyll, the green magnesium-containing compound in plants. Nearly all edible plant juices are anti-mutagenic in different degrees but the anti-mutagenicity is generally destroyed by cooking [79]. Anti-mutagens are important because today there is no possibility of eliminating all exposure to mutagens. A report from ICPEMC in 1986 said [76]:

> "In view of the widespread occurrence of mutagenic compounds in food and beverages as well as in other parts of the environment, effective elimination of exposure to many genotoxic chemicals is not feasible."

A study supported by the Dutch and United States Governments concluded that the most important mutagens in diet are the product of over-heating protein [80]. Fried beef, for example, results in a major increase in mutagens in blood and urine, illustrated in Figures 9 and 10. These show mutagenic activity of urine of one man following fried beef for lunch and for dinner [81]. The Japanese National Cancer Centre has been advising the public repeatedly for more than 10 years not to overheat protein [82]. Meat should be boiled or braised or steamed or cooked in a micro-wave oven without browning. The anti-mutagens in fresh vegetables and fruit are effective in different degrees against the mutagens in overheated protein [78]. Mutagens and carcinogens in food were the subject of a 200-page special number of Mutation Research in 1991 [83].
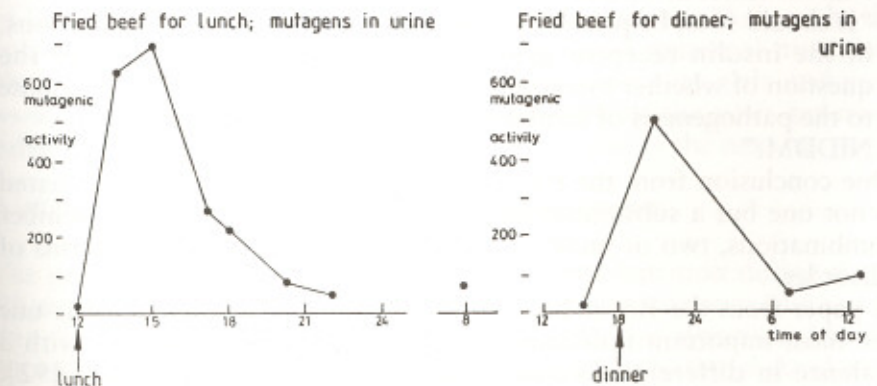
Figures 9 and 10. Reference 81

Low birth weight, genetic damage and disease in adult life

The opening of this paper discussed the association between low birth-weight and birth defects in children, and the association with cerebral palsy was illustrated in Figure 1. It has been shown in the United Kingdom, Japan and U.S.A. that low birthweight in animals can be produced experimentally by exposure of germ cells to mutagens in males or females before mating. In other words, low birthweight can result from mutation in the genome in males or females before mating[85-88]. This is the subject of a recent review paper from ICPEMC [89]. In summary, both from animal experiments and from human observations, it appears that slow-down in growth leading to low birthweight is often associated with a raised mutation rate – increasing the risk of mutational damage in offspring. And we have seen that the effects of poor maternal nutrition on growth are at least partly mediated by depression of hormone levels – which also increases mutation rate.

Professor DJP Barker and colleagues, of the MRC Environmental Epidemiology Unit, have shown a strong association between low birth-weight and subsequent non-insulin dependent diabetes mellitus (NIDDM) in later life [2]. There is also very good evidence that NIDDM has its origin before conception, from studies of monozygotic twins with origins in a single ovum [90]. How can low birth weight, an indicator at birth, be related to a pre-conceptional disorder? These different studies seem to be easier to reconcile if *both* the diabetes and the low birthweight had their origins during the follicular phase before ovulation. This conclusion is reinforced by a growing literature on mutations in the insulin gene and in the human insulin-receptor gene. A paper from the laboratories of the US National Institutes of Health says [91]:

> "It should soon be possible to determine the prevalence of mutations in the insulin receptor gene. These studies will also answer the question of whether mutations in the insulin-receptor gene contribute to the pathogenesis of insulin resistance with common forms of NIDDM."

One conclusion from the research so far is that NIDDM is associated with not one but a substantial number of mutations and a great number of combinations, two or more at a time, causing many different forms of the disorder.

A paper from the Royal London Hospital says that, "NIDDM is one of the most important non-communicable diseases in the world" with a prevalence in different countries ranging from 2 to 30 per cent [92]. NIDDM alone should focus attention on the importance of normal devel-opment during the follicular phase: development which can be encour-aged and protected by good nutrition before conception. A paper from the US Environmental Protection Agency says about toxic drugs [93]: "The greatest risk to the oocyte occurs on the days just prior to ovula-tion." There is every reason to suppose that this is also true of defective maternal nutrition. A review paper by Barker ends by saying (p 238 of reference 2):

> "We can reasonably suspect that the seeds of ill health in the next century are being sown today wherever girls and mothers have nutritional deficiencies whose nature we do not know."

Barker and his team have also shown that there are associations between low birthweight and death rates in middle age, although these studies also suggested that poor nutrition or illness during the baby's first year of life was a contributory factor. It is not known how far the low birthweight in these cases was of pre-conceptional, follicular origin; but it seems likely, if only from the data on diabetes, that much of it was. A report of ICPEMC in 1983 referred to diabetes as partly caused by new mutations [65]. What is new is Barker's association of early growth retar-dation with subsequent NIDDM, ischaemic heart disease and obstructive lung disease in middle age, pointing to poor maternal nutrition as a con-tributory factor in these disorders [2]. These new studies also add to ICPEMC's evidence that early growth retardation and low birthweight are often accompanied by a raised mutation rate [89]. Such findings prompt questions about the common causes of low birthweight and many nervous system disorders like spastic diplegia.

The influence of maternal nutrition on human mutation rates is a new and expanding chapter but can only be briefly introduced; it may in the end be the most important chapter of the subject because of the long-term inter-generational consequences. If things go wrong right at the beginning of life, and involve damage to the genome, it is always likely to be diffi-cult or impossible to find a remedy later. Good maternal nutrition is always likely to be cheaper. A nation which feeds its girls and young women well will have fewer men and women in the next generation suffering from disorders of mutagenic origin – and in the next but one.

A diet for women in their reproductive years

The greatest change in the teaching of maternal nutrition during the last 20 years has been the increasing emphasis on the importance of a satisfac-tory diet when *planning* a pregnancy. In 1970, the report on Maternal Nutrition and the Course of Pregnancy of the US National Academy of Sciences recommended daily folic acid supplements for all women during

pregnancy. Since 1991 all women who are *planning* a pregnancy have been advised by the British Departments of Health to take folic acid supplements [49].

There are, of course, many disabilities not associated with faulty nutrition. Good nutrition before pregnancy reduces risks but provides no guarantee. Many trials of dietary supplementation after diagnosis of pregnancy have produced only modest improvements in birth dimensions and have disappointed their sponsors [94]. The best we can say is that mothers who have babies who are well-grown and enjoy good health may be assumed to have had diets compatible with this good outcome. A diet aimed at prevention must begin before pregnancy, and the report on Maternal Nutrition of 1970 quoted with approval "the concept of protective diets for girls through adolescence to provide a sound physiological basis of pregnancy".

The protective diet should, of course, be continued through pregnancy. During the latter half of pregnancy the fetus is, however, highly protected by the placenta which can, for example, extract and concentrate vitamins from the mother's blood stream for the benefit of the fetus. The mother

Table 3: Suggested MODEST-BUT-ADEQUATE STANDARD of nutrition for women of reproductive age

Nutrient	nutrient density per 1000 kcal	daily nutrient intake
protein g	36.9	73.8
total fat g	38.1	76.2
saturated g	13.1	26.2
monounsaturated g	13.3	26.6
polyunsaturated g	9.1	18.2
fibre g	13.4	26.8
vitamin A ret equiv mg	574	1148
thiamin B1 mg	0.8	1.6
niacin equiv B3 mg	14.0	28.0
pyridoxine B6 mg	0.8	1.6
folate B9 mg	132	264
vitamin C mg	32	64
vitamin D mcg	2.0	4.0
vitamin E mg	5.0	10.0
calcium mg	464	928
iodine mcg	85	170
iron mg	6.5	13.0
magnesium mg	180	360
selenium mcg	24	48
zinc mg	7	14
Energy kcal per day		2000

% energy from protein: 14.8   % energy from fat: 34.3

Sources: References 4, 11, 19

can suffer from a manifest deficiency without the fetus being affected. The growth of the fetus during the last half of pregnancy increases demands on the mother which the placenta ensures are met except in cases of the most severe malnutrition. If the mother's diet is not adequate during the latter half of pregnancy it is primarily the mother's health that suffers. The fetus is protected by the placenta – but before the formation of the placenta the oocyte, ovum and embryo are more directly dependent on the nutrients and hormones in the maternal circulation.

What nutrients should then be found in a diet before pregnancy? There is one sound principle, that dietary recommendations should be based on the recorded diets of healthy people. French recommendations are based on this principle and describe the average diets of individuals "bien portants": expressly excluding individuals not enjoying good health, or suffering from any kind of metabolic abnormality, or living or working in a special environment [95]. In the context of childbearing, this principle means that dietary recommendations should include a category for women planning a pregnancy based on the recorded diets of women who had healthy babies in the optimal birthweight range.

In the Hackney Study the median protein intake of 165 mothers of babies in the optimum birthweight range was 73g/day [47]. This may be checked against data from other surveys. The US Institute of Medicine published a reference book in 1990 entitled Nutrition during Pregnancy which included a table of the nutrients in the diets of pregnant women from 17 different surveys [96]. Thirteen out of the 17 showed average maternal protein consumption in excess of 73g/day and the lowest average, for Mexican-Americans, was 68g/day; all these averages included some mothers of babies below optimum weight. No evidence has been found that maternal protein consumption higher than 73g/day has any merit. The COMA report has a much lower recommended RNI for women of reproductive age 15 to 50 years of 45g/day, but without any supporting evidence [24]. The evidence cited here suggests that the RNI is too low.

A modest-but-adequate dietary standard for women

A new and important standard, the modest-but-adequate family food budget, has been defined by the Family Budget Unit (FBU) centred on the University of York [97]. The Joseph Rowntree Foundation, which financed the work of the Unit over several years, presented their 17 Working Papers to a press conference on 10th November 1992. The expert groups on each item (for example food, housing, clothing, leisure) had the help of experts in other universities and institutions. Our recom-

mendations in Table 3 are based on the food budget of the Family Budget Unit, with some additions and modifications.

The modest-but-adequate diet might perhaps better have been called "adequate but modest". It is intended to be adequate for good health, but in the words of the FBU report, it achieves "a balance between health promotion and acceptability". The basic data indicating acceptability were provided by the National Food Survey (NFS) and Family Expenditure Survey (FES). The FBU recommendations are similar to the French recommendations, although based on British data. The "modest" refers to a choice of foods at modest cost to provide the desirable nutrients: that is no partridge instead of chicken; no expensive cuts of meat, nor Roquefort instead of Cheddar cheese, nor pineapples instead of plums. The nutrient densities, expressed as nutrients in food per 1,000 kilocalories, for the different nutrients in Table 3 are based on those for the family of two adults and two children; nutrient densities in practice vary very little with family composition. It was thought essential, however, to compare the diet so devised with the diets of women in the Hackney survey who had babies in the optimum birthweight range. The diet was thus adapted in some details towards a diet satisfactory for child-bearing. A comparison was also made with French, Swedish and Japanese recommendations, which are similar to those based on the FBU recommendations. The Swedish recommendations were then followed for pyridoxine, vitamin E, magnesium, zinc and selenium, essential nutrients known to influence childbearing but not recorded by the FBU.

It has been assumed in Table 3 that women require a daily energy intake of 2,000 kcal. This is close to the median value of 1,983 kcal/day reported in the Hackney study for pregnant women towards the end of the first trimester [54]. In fact the actual energy requirements of individual women vary widely.

There is one very practical reason for specifying nutrient density in nutritional recommendations. More and more catering today is done under contract, often with competitive tendering. Contracts require specifications, which are simpler and easier to control if expressed in terms of nutrient densities.

An optimum level of essential nutrients

The nutrients most associated with birthweight may be listed, but there is a very important qualification. When mothers in the Hackney study were divided into two groups by the weight of their babies (above and below the median of 3,270g) an important discovery was made. Mothers of the larger babies, above median weight, ate more than the mothers of the smaller babies; but the weight of babies did not go on increasing with higher food intakes above the median weight of 3,270g. The mothers with the larger babies had, in effect, reached saturation values for all nutrients recorded. It is not possible to make babies bigger and bigger by eating more and more. In contrast for mothers whose babies were below the median weight of 3,270g there was a highly significant association between maternal nutrition and size of baby. Babies became on average smaller and smaller, as their mothers ate less and less.

Apart from protein there were 12 nutrients in the maternal diet in Hackney very significantly correlated with birthweight: 5 minerals and 7 B vitamins. Order of importance can only be based on the particular diets of the Hackney women and is special to that study. Of the minerals, magnesium had the highest correlation with birthweight of any mineral (and indeed any nutrient), followed by iron, phosphorus, zinc and potassium. The 7 most significant vitamins followed: all belonged to the B group, and they were thiamin, niacin, pantothenic acid, riboflavin, folic acid, pyridoxine and biotin.

The Hackney study showed the main differences in food choices. Many mothers of the small babies had no breakfast. Mothers of the larger babies ate more breakfast cereals, muesli, oats, nuts, seeds, eggs and wholemeal bread, which explained some 40 per cent of the higher intake of B vitamins and minerals. Mothers of the small babies also consumed less dairy produce, vegetables and fruit. Meat did not seem to be a limiting factor in this population.

Continuing Caroline's work

We began this paper with the title "No nation can rise above the level of its women." Caroline wrote: "If the next generation is to rise, rather than fall, it is essential that children are supplied with food which will enhance their health" [98]. In the book written with Caroline, Geoffrey Cannon recalls the television programme following the publication of a report on diets of British school children [99]. There were the mounds of chips, the cans of soft drinks, the packets and packets of biscuits, dishes of cakes and the little group of fruits and vegetables. She concluded, "it shows to anyone with a training in nutrition that children are eating highly processed, unhealthy food. It shows that we are storing up an enormous problem for ourselves as a nation". School girls are future mothers. We suggest that our table of nutrients and nutrient densities, making up the modest-but-adequate food budget for women in their reproductive years (Table 3), should be used for school children including boys as well as girls. How well we feed girls in school does not only affect their health

Table 4: Wheat products as a source of those nutrients in the maternal diet most related to birthweight

Nutrients per 100g	wheatgerm	wholemeal bread	white bread	digestive biscuits
magnesium mg	270	76	24	23
iron mg	8.5	2.7	1.6	3.2
phosphorus mg	1050	200	91	88
zinc mg	17	1.8	0.6	0.5
potassium mg	950	230	110	170
thiamin mg	2.01	0.34	0.21	0.14
niacin mg	4.5	4.1	1.7	1.1
pantothenic acid mg	1.9	0.6	0.3	–
riboflavin mg	0.72	0.09	0.06	0.11
folic acid mcg	331	39	29	13
pyridoxine mg	3.30	0.12	0.07	0.09
biotin mcg	25.0	6.0	1.0	–

but influences their food choices and habits in their child-bearing years. If future mothers are not well fed, through choice or because of the stresses of life and income, the next generation will carry a burden of ill health and disabilities which could have been avoided. Nations rise and prosper by the capacity and ability of succeeding generations. We have suggested that a new chapter should be added to the great subject of maternal nutrition: the effect of maternal nutrition on the genetic inheritance. The book of maternal nutrition should today include also a chapter on the nutrition of girls in anticipation of childbearing.

Caroline Walker was surely right in linking the ubiquity of junk foods with the grand sweep of national health. May we suggest that the Trust and other food researchers might take as a subject of study types of food currently poor in minerals and vitamins – and unnecessarily so – and see if they can produce lists of best buys, and recommendations to manufacturers, with new angles on the product?

We suggest biscuits as a first target. The Trust and other campaigners could espouse a Better British Biscuit. Biscuits have an honourable ancestry in the oatcake, barley cake and other dry cereal cakes for the huntsman, the farmer, the traveller, the school child. They need water, a little fat and some flavouring or sweetening. The Dietary Survey of British Adults showed that 80 per cent of women eat biscuits; the great majority of children also eat biscuits, which are a useful source of calories. They are also an end-product of that degradation of natural foodstuffs which

Caroline so passionately and eloquently condemned. In her famous account of a Christmas hamper, she found 30 ingredients in Teatime Assorted [98]. The 12 nutrients associated with birthweight are listed in Table 4 and the amount of these nutrients is shown in wheat germ, in wholemeal flour, white flour and a popular biscuit. From the natural raw ingredients to the biscuits in the packet the processing reduces the concentration of every one of the 12 nutrients that we have seen to be important in maternal diet; in some cases to very low levels. Note in contrast how the concentration of all these 12 nutrients is increased in the wheat germ – in the proximity of the wheat's own genome.

Biscuits are only an example of foods that could be greatly improved. Perhaps, too, we should give more attention to the way food is damaged not only by the manufacturer but in the home. The browning and burning of protein in hot fat does seem to produce some very mutagenic substances. Better biscuits and better protein cooking may seem small steps in the grand cause of improving the nutrition of one generation in order to improve the health of the next. But progress is made by long series of such small steps. As Caroline wrote: "If we care about our health, and the health of the next generation, we should remember that good food is fundamental to good health."

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