Twenty-five years have elapsed since the conference on ‘Malnutrition, Learning and Behavior’ was held at MIT in 1967. This was an international meeting attended by scientists from thirty-eight countries and gave rise to a highly influential book, which proved to be the cornerstone for research in this field for the ensuing quarter century (Scrimshaw & Gordon, 1968). That was also the time when I entered this field, first with an isolated piece of research conducted in Glasgow with Tony Barnett in collaboration with Elsie Widdowson (Barnett et al. 1971) and then more intensively when I joined John Dobbing in Manchester in 1969.

It is clear from re-reading Malnutrition, Learning and Behavior (Scrimshaw & Gordon, 1968) that most of the important issues had surfaced by 1967 and were appreciated in principle by at least some of the participants. Herb Birch’s (1968) contribution is full of insight and should still be required reading for any serious student of the subject; and yet a few of his arguments now seem wide of the mark. He opens his chapter: ‘Since the time that Goldberger identified the nutritional etiology of a syndrome characterized by dermatitis, dementia, and diarrhea (pellagra), there has been little doubt that nutritional status is related to mental and behavioral functioning. . . . It is no longer useful to ask so general a question as “Does malnutrition relate to behavioral development or to mental capacity?” We must ask (1) What kinds of nutritional deficits, suffered at what stages of development, are systematically associated with defined aspects of behavioral competence? (2) Are the obvious behavioral and intellectual abnormalities noted in acutely and severely malnourished children transient or persistent?’ The problem here was the unwarranted jump from the effects of a specific nutrient deficiency to those of generalized protein–energy malnutrition. Also his ‘. . . obvious behavioral and intellectual abnormalities noted in acutely and severely malnourished children . . . ’ are better regarded as symptoms of clinical disease rather than proof of an association between nutrition and behaviour. Indeed, the question which Birch (1968) dismissed, ‘Does malnutrition relate to behavioral development or to mental capacity?’ has continued to exercise researchers over the ensuing 25 years and has proved enormously difficult to answer.
The great problem, of course, is that malnutrition is usually born of poverty and, hence, is likely to occur in association with numerous other factors which are disadvantageous for development. The investigator is faced with disentangling the contribution of nutrition from that of the other negative factors. One approach has been to compare malnourished children with 'control' children matched as far as possible for socio-economic status with the malnourished children but with no history of malnutrition. The results of some such studies have been highly suggestive of impaired performance due to previous malnutrition (Hertzig et al. 1972; Galler et al. 1983), but the doubt always lingers that the matching may not have been entirely satisfactory. Birch (1968) strongly recommended studies of the prospective type and, indeed, some recent investigations which have been wholly or largely prospective in nature have provided some of the most compelling evidence of nutritional influences on behavioural development (Lucas et al. 1990; Grantham-McGregor et al. 1991; Husaini et al. 1991). Other features of these 'successful' studies were that:

(1) they involved children who were at risk of inadequate nutrition;
(2) some form of dietary supplementation was employed;
(3) they utilized a randomized clinical trial type of experimental design; that is, subjects (or centres) were ascribed to treatment groups randomly.

In fact, the first of these studies was not specifically an investigation of early malnutrition at all, but was a comparison of different nutritional regimens for preterm babies (Lucas et al. 1990). This is a large and rather complex study involving about 1000 preterm babies (birth weight <1850 g) at five centres in England. As part of this study about 400 babies were assigned to one of two groups given either a 'term' formula milk or a preterm formula enriched in protein, energy, macrominerals and trace nutrients to meet the calculated increased requirements of preterm infants. They remained on these formulas for an average of 4 weeks. The subsequent nutrition of the babies was not under the researchers' control and varied randomly between groups. At 18 months post term those babies previously fed preterm formula were found to have major developmental advantages which were more so in motor than in mental function. For the motor development index the advantage was a full fifteen points, about one standard deviation. Follow-up at 7.5-8 years is currently under way and the results are eagerly awaited.

It could, of course, be argued that this association between early diet and subsequent development is specific to preterm babies and should not be extrapolated to term babies or older infants. After all, the preterm baby would be a fetus under normal circumstances, nourished via the placenta. The second piece of substantial evidence of an association erodes this criticism, since it deals with the effects of nutritional supplementation commencing well into postnatal life (Grantham-McGregor et al. 1991).

The subjects under study were Jamaican children who were identified by their small stature at 9-24 months of age as having suffered from malnourishment (length/height <−2 SD of reference means). The study was designed to investigate the benefits of nutritional supplementation, with or without psychosocial stimulation, and to this end the children were assigned to four groups; control, nutritional supplementation, stimulation and both interventions. The supplement comprised 1 kg milk-based formula/week for 2 years, and the stimulation involved weekly play sessions at the home with a community health aide. Development (DQ) was assessed on the Griffiths Mental Development Scales at six-monthly intervals over the 2 years of supplementation. Both
supplementation and stimulation were found to have independent beneficial effects on the children's development. These were additive, with the combined interventions more effective than either one alone. However, some abilities benefited more than others. For instance, supplementation boosted locomotor development by 12-4 points, but hand/eye development by only 2-2 points. Overall, these findings suggest strongly that slow behavioural development in stunted children is at least partly attributable to under-nourishment.

Another recently published study along the same lines supports the same conclusion (Husaini et al. 1991). The present study assessed the developmental effects of supplementary feeding over only 90 d on infants aged 6–20 months at six tea plantations in West Java, Indonesia. Previous research had established that such children are nutritionally at risk. Every day except Sunday the children attended one of twenty day-care centres. Nine of the centres were randomly assigned as supplementary feeding centres and eleven as control centres. Supplementation provided an average of 10-66 kJ and 5 g protein/d. The Bayley Scales of Infant Development were administered before and after the period of treatment and revealed that supplementation enhanced scores substantially on the psychomotor development index but not on the mental development index.

I should like to make a few general comments about these studies.

(1) They provide the most reliable evidence so far of an association between early diet and behavioural development in man. Their success would appear to be due to use of the clinical trial type of experimental design, which is unprecedentedly rigorous in this field of research.

(2) The question of how lasting the effects may be remains open. Only in the investigation of preterm babies were effects sought after the period of dietary treatment (Lucas et al. 1990). In the other two studies development was assessed before, during and at the end of nutritional supplementation (Grantham-McGregor et al. 1991; Husaini et al. 1991). There is clearly a need for follow-up studies and, indeed, the preterm baby project is continuing.

(3) It is of interest to consider whether these findings impinge on a question which has permeated research on early malnutrition and behaviour since its beginnings: if there are demonstrable effects of early nutrition on behavioural development, are they mediated through effects on brain growth? The findings for preterm babies appear to support the affirmative conclusion, in that 4 weeks on the preterm formula has parallel enhancing effects on behavioural development (Lucas et al. 1990) and on head circumference (Lucas et al. 1984), which is thought to reflect brain size. It is also worth wondering why such a short period of dietary treatment should have such an impact detectable more than 18 months later. The clue might be in the timing of the treatment, which is at an early stage in the human brain growth spurt when there is more neuronal and less glial cell proliferation than later on (Dobbing & Sands, 1973). Restriction of neuronal numbers may well be more serious than that of glial.

(4) One of the clearest conclusions from the three studies is that motor development is much more affected by early diet than mental development. Both giving the enriched preterm formula (Lucas et al. 1990) and, later, postnatal supplementation (Grantham-McGregor et al. 1991; Husaini et al. 1991) result in advanced motor development. Furthermore, there is other evidence of the same phenomenon (Joos & Pollitt, 1984). It is not at all clear why this should be, and a number of explanations come to mind which
differ widely in the extent to which they involve the central nervous system. The phenomenon could be due to one of the following:

(a) less mature muscular or neuromuscular development in the poorly nourished; certainly, animal studies provide ample evidence of gross deficits in muscle growth resulting from early undernutrition (Bedi et al. 1982);

(b) brain development may be relatively immature in those regions known to be involved with motor behaviour, such as the cerebellum;

(c) nutritional lack may slow the attainment of threshold levels of ‘brain activation’ for the mobilization of specific behaviours (Husaini et al. 1991);

(d) the general lassitude associated with malnutrition may result in a failure in the practising of motor skills which leads to the development of new motor skills.

One has to admit that this multiplicity of possible interpretations is unsatisfactory and also that it is typical of this field of research.

ANIMAL STUDIES

Problems with the animal models and implications for mechanisms

1. Side-effects of the undernutrition procedures. Back in 1967 there was considerable faith that animal experiments would be more successful than human studies in elucidating the effects of early undernutrition in a manner that would be incontrovertible. They offered a ‘pure’ model with the completeness of control over the situation that the field researcher could not hope to attain (Smart, 1984). However, even in 1967 the seeds of doubt were there to be seen even if they had not actually started to grow. Slávka Fraňková (1968) had started to consider and to manipulate aspects of the environment of underfed rat pups. Thereafter, in the ensuing decade, the realization that the animal model was not as pure as had been hoped took firm root.

The problem arises because of the desire to undernourish the developing animal during its brain growth spurt in order to produce the greatest effect on brain size and, hence, it was argued, on behaviour. In the most popular experimental subjects, rats and mice, the brain growth spurt largely coincides with the sucking period, and so that was when undernutrition was usually imposed. All the various methods employed sought to restrict the amount of milk available to the pup and inevitably involved the mother. Plaut (1970) was the first to point out that it was highly likely that the various procedures would produce a different physical and social environment for the undernourished pup. Evidence to back his suggestions soon followed (for review, see Smart, 1983), in particular, findings of altered mother–infant interaction and, especially, of greater maternal contact enjoyed by undernourished young. Unfortunately, these sorts of side-effects of the undernourishment procedures could of themselves influence the development of behaviour. Levine & Wiener (1976) concluded that ‘...the disruption of the animal’s early environment may, in part, be responsible for the differences in later adult behavior that have been attributed to malnutrition’ and further that ‘It will be necessary to derive an animal model in which malnutrition can be produced with a minimum of disturbance of other environmental conditions.’ Numerous worthy efforts were made to produce a model which ensured equivalent maternal care for well-fed and underfed young. For instance, Slob et al. (1973) and Lynch (1976) devised ingenious variations on the method in which pups are undernourished by separating them from
their mother for several hours daily. Rather than merely keeping the pups warm in an incubator during the separation, they put them in the care of a non-lactating ‘aunt’ (Slob et al. 1973) or with a mammeectomized female which had recently carried a litter to term (Lynch, 1976). ‘Muzzling’ individual pups within a litter for part of the day to prevent sucking was also tried (Misanin et al. 1979).

However, it seemed to me that all these attempts to ensure equivalent maternal care were doomed to failure, since the quantity and quality of maternal attention depend to an important degree on the condition of the pup itself: its size, state of maturity, etc. (Smart, 1980). The only solution appeared to be to remove the mother from the situation altogether and to rear the pups artificially.

2. The artificial-rearing approach. I contemplated artificial rearing as far back as 1968, and there probably still exists in some MRC basement the grant application that I wrote, preparatory to starting work in Manchester, in which I advocated this procedure. However, I did not put my suggestion into practice for a number of years, partly because I was concerned to establish reliable, lasting behavioural effects of early undernutrition, and partly because the existing methods of artificial rearing were technically difficult and were not particularly good in terms of the subsequent survival and growth of the pups (Thoman & Arnold, 1968; Messer et al. 1969). The advent of a much more elegant artificial-rearing technique (Hall, 1975) encouraged me to go ahead and put the idea into practice (Smart et al. 1981).

Essentially, the technique is to fit rat pups of a few postnatal days of age with a gastric cannula, through which milk or a milk substitute can be delivered automatically by infusion. Even with Hall’s (1975) improved method, this is a labour-intensive and demanding technique, with which much can go wrong. This probably explains why only my laboratory has used it in the context of early undernutrition research. But we persevered, modifying the method further still, and were eventually able to apply it to our particular questions in a series of experiments (Tonkiss et al. 1987; Smart et al. 1989). The experimental design utilized four groups of rats: two artificially-reared, well-fed and underfed, and two corresponding mother-reared groups. Undernutrition was from five to twenty-five postnatal days (suckling and early post weaning), after which all rats were fed ad lib. and eventually subjected to a variety of behavioural tests as adults.

To summarize the findings, the effects of undernutrition were similar whether the pups had been mother-reared or artificially-reared and even tended to be more pronounced in the artificially-reared animals. The implications are twofold: (1) the effects in the artificially-reared animals cannot have been maternally mediated and, hence, it is highly likely that they were due to a direct effect of undernutrition on the developing animal, perhaps by influencing brain growth and development; (2) the tendency to greater effects of undernutrition in the artificially-reared animals suggests that any altered maternal care enjoyed by the mother-reared underfed animals may have been beneficial to them; perhaps actually buffering them from the worst effects of the undernutrition.

Functional isolation hypothesis

In parallel with concerns about indirect effects of undernutrition procedures and their possible contribution to the mechanisms mediating the effects of early undernutrition on behaviour, there evolved another theory concerning mechanisms: the ‘functional isolation hypothesis’; literally that the undernourished animal is functionally isolated.
from its environment. The train of thought which gave rise to this was probably sparked off by Fraňková's (1968) demonstration that giving undernourished rat pups additional stimulation ('gentling' by the experimenter) appeared to counteract the effects of the undernutrition on behaviour. Further experiments at Cornell confirmed this finding and considerably extended it: stimulation during and after the period of undernutrition ameliorated the effects on a range of behaviours tested several weeks later (Levitsky & Barnes, 1972). Three possible mechanisms were suggested in that paper but, latterly, David Levitsky came to favour one of them. The following statement encapsulates the hypothesis: 'Early malnutrition causes long-term effects on behavior, not by altering the gross physical structures of the brain such as total brain DNA or myelin content, but rather by changing the kinds of information the young animal acquires about its environment' (Levitsky & Strupp, 1984). The reasoning from findings to hypothesis seems to me rather odd: because stimulation improves matters, then the important effect of undernutrition is to render the animal deficient in picking up information from its environment. (Rather like arguing that since penicillin cures a diseased animal, the disease was caused by lack of penicillin.) Nevertheless, questionable logic or no, the hypothesis gave rise to a number of experiments which support the idea that undernourished animals utilize information available to them in their environment less efficiently than well-nourished animals. Most of these experiments involve 'latent' learning, also known as exploratory, exposure or redundant learning: learning which is not manifest at the time at which it occurs. This learning is not required or rewarded when it occurs, but can be advantageous later.

Undernourished rats have been found to be deficient in this kind of learning when the exposure phase has occurred while the animals were still in a state of undernutrition (Levitsky & Strupp, 1984). The subsequent demonstration of deficient latent learning is perhaps not surprising if, at the time of the exposure, the undernourished animal was in a state which was incompatible with registering information from its environment: perhaps lethargic and apathetic or hyperactive, depending on the severity and nature of the nutritional privation. However, there is also evidence suggesting lasting impairment of this kind of ability. Latent learning was found to be impaired in experiments in which the exposure phase occurred some weeks after the period of undernutrition (Katz et al. 1979). There the interpretation is more difficult. As well as functional isolation in Levitsky's sense, other possibilities need to be entertained, such as deficiency of perception or in some memory process resulting from altered brain structure or function.

Conclusions regarding causation

Much of this section on animal studies has been concerned with the question of causation: what are the mechanisms mediating the effects of early life undernutrition on behavioural development? The first suggested, and most direct, nutritional mechanism relates undernutrition to subsequent behaviour via nutritional restriction of brain growth and development. In essence, shortage of material leads to sub-standard structure and ultimately to deficient output of that structure. Then the behavioural scientists pointed out that the situation was much more complex and embodied numerous side-effects which might themselves influence development (for detailed discussion, see Smart, 1987). The problem has been to know what weight to give the word 'might'. Fig. 1 illustrates my appraisal of the situation.
It seems to me that the central direct route stands firm, on the evidence both of the artificial-rearing experiments with rats and the recent human studies. However, it must be said that it will probably be impossible ever to separate the suggested effects of functional isolation from those of altered brain growth and development. Functional isolation could be an inevitable concomitant of the undernourished state. It is difficult to think of anything better than indirect or circumstantial evidence ever being brought to bear on the attempt to disentangle the two. Whether or not it matters depends, I suppose, on whether a satisfactory answer would be helpful in identifying the most appropriate remedial treatment.

Other messages from animal studies

1. **Vulnerable periods.** The question has often been posed: ‘When is the animal most vulnerable to undernutrition?’ In response, evidence has been gathered and a number of hypotheses proposed. These have usually related to specific processes or systems (Widdowson & McCance, 1963; Winick & Noble, 1966; Dobbing, 1968), although this has not inhibited incautious extrapolation.

   Restricting the present consideration to mental development, the available evidence would appear to support the hypothesis: ‘the earlier, the worse’. Table 1 reviews the results of 137 experiments on rats (Smart, 1986) and indicates that performance in tests of learning is much more likely to be impaired if the period of undernutrition includes gestation.

   This conclusion is paralleled by the findings of the preterm baby study (Lucas et al. 1990): even a brief period of inadequate nutrition in what should be fetal life can have marked consequences for subsequent development. A likely explanation has already been mentioned involving the predominance prenatally of neuronal rather than glial cell proliferation in man and the rat, with glial multiplication occurring largely postnatally (Dobbing & Sands, 1973). It seems plausible to suggest that nutritional restriction of the number of neurons would have the more serious consequences for mental development.
Table 1. Numbers of experiments indicating superior performance by well-nourished control (C) or previously undernourished (PU) rats or no significant difference, relative to the timing of the undernutrition (from Smart, 1986)

<table>
<thead>
<tr>
<th>Period of undernutrition</th>
<th>Total</th>
<th>Where C superior</th>
<th>Where PU superior</th>
<th>Where no significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation</td>
<td>16</td>
<td>9</td>
<td>0**</td>
<td>7</td>
</tr>
<tr>
<td>Gestation and sucking</td>
<td>38</td>
<td>22</td>
<td>1**</td>
<td>15</td>
</tr>
<tr>
<td>Sucking</td>
<td>60</td>
<td>19</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>Sucking and early post-weaning</td>
<td>17</td>
<td>9</td>
<td>1*</td>
<td>7</td>
</tr>
<tr>
<td>Early post-weaning</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01 (Sign test, two-tailed, comparing observed frequencies with the null hypothesis, equal frequencies of C and PU superiority).

Incidentally, the occurrence of such an early period of vulnerability as this would appear to support the ‘direct route’ mechanism for the effects of early undernutrition rather than functional isolation.

2. Effects differ markedly from one ability to another. This conclusion emerges clearly from an extensive review of research on the effects of early undernutrition on subsequent learning ability in rats (Smart, 1986). For instance, there was no consistent evidence of impairment in active avoidance or position learning, whereas visual discrimination and learning to negotiate complex mazes were much more reliably affected.

Castro & Rudy (1989) have recently elucidated this phenomenon by investigating the progress of recovery in function after early undernutrition. They explored the extent to which the abilities to make certain discriminations recover during refeeding. At one extreme, position discrimination was normal at all ages; at the other, pattern discrimination remained impaired even at the latest age tested. But in some respects brightness discrimination was the most interesting: soon after the commencement of refeeding the formerly undernourished rat pups could not solve the discrimination at all, 3 weeks later they were able to do so but not as efficiently as their well-fed controls, and a further 7 weeks later they showed no residual impairment.

The apparently greater vulnerability of psychomotor development which has been noted in human studies (see pp. 191–192) probably reflects this same phenomenon of differential susceptibility. There may be a case for finer-grained analysis of test results from children (usually reported as global or major category scores) to attempt to identify which specific abilities are the most impaired and to investigate these more intensively.

3. Individual x environment interaction. The possibility that different individuals may respond differently to a particular environmental stressor, here undernutrition, seldom seems to receive more than token acknowledgement in spite of clear confirmatory evidence. For instance, genotype x undernutrition interactions have been found whenever they have been sought (Tonkiss & Smart, 1983a); that is, different genetic strains or stocks of animals differ in their degree of response to early undernutrition. Whether there were lasting effects on a variety of different behaviours was found to depend to an important extent on the genetic stock of the animals concerned (Tonkiss & Smart, 1983b).
Phenotype x environment interaction is also a possibility. Phenotype in this context would be the animal's condition, a product of its genes and the environment in which it has developed, at the time of the nutritional insult. A nice example of this type of interaction is the greater effect of diet in preterm babies who are born small for gestational age rather than appropriate for gestational age (Lucas et al. 1990).

Researchers in this field would do well to be alive to the possibility of such interactions, which are interesting in their own right and which may account for an important proportion of the variance in results.

4. Social behaviour. Perhaps the most reliable lasting effects of early life undernutrition in experimental animals are on various aspects of social behaviour (for review, see Smart, 1981). For example, formerly undernourished male rats are more aggressive to one another than are well-fed controls. However, I suggest no qualitative correspondence of such effects in man whatsoever; the development of social behaviour is too complex and to a considerable extent it is species-specific. I merely suggest that it would be well worth assessing in man. In the few cases in which attempts have been made to do so, effects have been found (reviewed by Barrett, 1987). The reason why such assessment is seldom attempted is, of course, that direct observation, as in animal experiments, is time-consuming and labour-intensive. However, alternative approaches are possible. Richardson et al. (1972) conducted a sort of popularity poll in school; and it would take only a little ingenuity to devise other interview or paper-and-pencil methods of assessment. Indeed, some assessment of personality type might be rewarding.

CONCLUSIONS

There seems to be more compelling evidence than ever before, especially from human studies, that early undernutrition impairs behavioural development. Whether this is mediated through effects on brain growth and development is still not conclusively proven, though several lines of evidence suggest that it is. Certain inevitable concomitants of undernutrition may also contribute.

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