Conclusions

The results of gross malnutrition and deprivation of foodstuffs can therefore be due to some of these individual nutrient deficiencies, in so far as animal results apply to man. They can be due to other individual dietary deficiencies, they can be due to the algebraic effect of several deficiencies. Still more, of course, gross deprivation of protein and fats can be expected to cause such a general depression of bodily activity and vigour that fertility will fall. These last effects have, however, not been analysed quantitatively, apart from factors such as lysine needed for growth in general.

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Nutrition and Human Fertility

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The influence of nutrition on reproduction, though extensively studied in the lower animals, has been the subject of few critical investigations in man. Widely divergent views are held, ranging from the completely sceptical to the unreasoningly enthusiastic, and the lack of fully substantiated basic data makes it difficult for the unbiased student to find the most probable of the several possibilities presented. The attempt of this paper will be to discuss a few aspects of this broad subject, the emphasis throughout being placed on probability.

Starvation

At the outset, taking a world view, one is faced with what appears to be a paradox: in the west the relatively well-nourished populations have in general a lower birth rate and tend to be static or declining, while in the east malnutrition is rife, but the birth rate is for the most part higher and the populations are expanding. Undoubtedly factors other than nutritional can be cited by way of explanation, and it is possible that the potential fertility of western populations might be far higher than the observed fertility; or again, that, were the eastern peoples well nourished, their reproductivity might be vastly greater than it is. It is clear, however, that long-continued suboptimal nutrition is not necessarily associated with reproductive failure, nor are periods of acute starvation necessarily followed by permanently impaired fertility, as is evidenced by the mere fact of survival of the human species.

On the other hand, the effect of such periods of starvation on reproduction has been well demonstrated at least twice during the present half-century and some recently published data are informative. Smith (1947) has described the effects of the severe

Table 1. *The effect of acute malnutrition on the birth rate in Rotterdam**

	No. of births per week in											
Year	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1939	Weekly average 206											
1944	228	214	234	231	227	227	228	227	245	238	218	210
1945	228	262	241	270	230	199	196	157	112	84	87	89

* From Smith (1947).

curtailment of food supplies to Dutch cities between December 1944 and April 1945, when the average energy and protein intake fell to 1100–700 Cal. and 35–25 g./day, respectively. Of the women 50 % suffered from amenorrhoea, 50 % of the remainder having menstrual irregularities. Nine months later the birth rate fell to one-third of its normal value (Table 1), and since the incidence of abortions and stillbirths was not obviously affected, it may be concluded that the impact fell primarily upon conception rate. When the food supplies returned to adequacy, the birth rate, nine months later, rose to 'unprecedented levels', revealing the very temporary nature of the starvation infertility.

A similar, or even more striking, result has been described by Antonov (1947) for the siege of Leningrad which lasted from August 1941 to January 1943, conditions being particularly severe from the time of encirclement in September 1941 to February 1942. Amenorrhoea was again found to be prevalent, and some idea of the effect on reproduction can be gained from the comparison of the average number of births for July–December of 1939 and 1940 with those for July–December 1942, 1798 and seventy-seven respectively. The fact that Leningrad was actually under bombardment may account for the disparity of these figures and those mentioned for Holland.

Obesity

Turning now to some specific aspects of nutrition in relation to fertility, it may first be stated that little is known of the precise effects of calories, protein, carbohydrates and fats, but two points, both applying to overweight, and therefore excessively nourished, women, are worthy of mention. Such women frequently have irregular or scanty menses and may complain of infertility. Though unfortunately no critical studies have been made, it is a matter of common clinical knowledge that weight reduction of substantial degree by suitable dietary measures is often followed by a re-establishment of menstrual regularity and, eventually, by conception. The probable explanation of this sequence of events is that the excessive fat depots remove so much of the circulating oestrogens (by reason of their solubility in fat) as to prevent their rhythmic fluctuations which are so fundamental an aspect of the menstrual cycle. In consequence, the normal pituitary-ovarian relationships are interrupted and ovulation ceases. When the fat depots are reduced their buffering action is diminished and cyclic pituitary-ovarian activity becomes re-established.

The second point relates to some recent observations by Barton & Wiesner (1948) on refractory 'cervical block' as a cause of infertility in overweight women between the ages of 30 and 40. Infection of the cervical canal was found to be frequent and, unlike that found in women of normal weight, failed to respond in the usual manner to antibiotics and oestrogens given in small doses in the proliferative phase of the cycle. Because *Bacterium coli* was the commonest organism found, these investigators tried the effect of substituting lactose for the sucrose of the diet, following the suggestion that such treatment would produce a more 'favourable' intestinal flora. They were surprised to find that this measure caused a loss of weight of about 1 lb. a week in nine out of twelve patients, in all of whom the cervical block was resolved, either immediately, or following the use of antibiotics and oestrone. That lactose had no specific action in this respect was next shown by the successful outcome, so far as the cervical block was concerned, in forty-five out of sixty-five patients taking the sugar-free diet but omitting the lactose. Finally, in a group of nine patients placed on a sugar-free diet but permitted supplements so as to make up for the energy lost by the exclusion of sugared foods, six lost weight and in all six cervical function was restored. It must be admitted that the precise manner in which dietary sucrose leads to the syndrome of genital infection, obesity and cervical block is quite obscure.

Vitamins

Most of the studies of nutritional aspects of human fertility have related to the vitamins. Controversy is keen on all points, and no attempt will be made to enter into it, beyond drawing attention to some aspects which have perhaps received less emphasis than they deserve.

The vitamin B complex. Taking the vitamin B complex first, there seems little doubt that in women deficiency can lead to profound effects on ovarian activity and thereby cause sterility. Biskind (1946) found a quite remarkable correlation between the signs and symptoms of nutritional deficiency and the occurrence of syndromes related to oestrogen excess, the basis for which he believes to be failure of the liver to inactivate oestrogens. Though it is most improbable that in this country the correlation would be anything like that claimed by Biskind, there can be no doubt that liver disease, such as cirrhosis, and some types of avitaminosis, such as pellagra, may be associated with menorrhagia. Peters & Footer (1945), moreover, have claimed that in patients with excessive uterine bleeding due to the persistence of an acyclic oestrogenic endometrium, the latter can become cyclic on vitamin B therapy and the menstrual flow thereby be reduced to normal proportions.

In the male also there is evidence that vitamin B deficiency may play a part in the genesis of infertility, the liver again being implicated. Thus, Glass, Edmonson & Soll (1940) found testicular atrophy in all of fourteen men with cirrhosis of the liver, and Biskind (1946) found testicular softening or atrophy in a high proportion of men with nutritional deficiencies, as indicated by a somewhat too comprehensive list of signs and symptoms. From the point of view of the treatment of male infertility, published work

Table 2. *Summary of the report by Biskind & Falk* (1943) *on the effects of vitamin therapy on twelve cases of male infertility*

	Semen				
Case no.	Volume (ml.)	Density (millions/ml.)	Motility (%)	Abnormal forms (%)	Fertility
1	2·2	20	50	45	Pregnancy
	No other analysis				
2	6	14	30	36	Pregnancy
	9	18·4	75	22	
3	2·6	190	Almost none	23	No pregnancy reported
	3·6	178	5	14	
	—	—	41	—	
	—	—	68	12	
4	0·9	2·3	70	30	No pregnancy reported
	4·8	9·2	64	31	
	3	31·5	90	25	
	4·7	41·7	—	—	
5–9	No seminal analyses or no improvement				Five pregnancies with one abortion
10–11	'Increase in the number of sperm and definite diminution in the percentage of abnormal forms'				No pregnancies
12	Extreme oligospermia: no improvement				No pregnancy

is less convincing. One of the most quoted papers on the efficacy of such treatment is that of Biskind & Falk (1943), and one is disappointed, on actually consulting it, to find, in the first place, that it concerns only twelve patients, with the seminal findings detailed in only four (Table 2). In no case were repeated analyses made before treatment and there is no doubt that variations similar to those published could have been obtained in untreated patients (Table 3). The extent of infertility, moreover, in several cases is most dubious; it covered 14 months of marriage to the onset of pregnancy in one case, 1 year of intercourse without contraception out of 6 years of marriage in another, and 1 year out of 3 years of marriage in a third. Five pregnancies occurred in cases wherein no seminal analyses had been made, or wherein no improvement was found; the authors have no right to claim these as due to vitamin therapy. From this, therefore, as from the few other papers on the subject, one cannot feel very impressed by the value of vitamin B complex therapy for male infertility.

Vitamin E. In respect of vitamin E and male infertility, reference will be made to three recent reports. Warren (1948) treated fifty cases of oligospermia with 30 mg. of vitamin E twice daily and found an increase in density in twenty-three cases, improvement in motility and viability in eighteen and an increase in volume of 0·5 ml. or more in seventeen. The percentage of abnormal forms was decreased in all cases where improvement in any other factor had occurred. Davidson (1948) treated forty-two

Table 3. *Random variations in seminal analyses from untreated men**

Patient no.	Density (millions/ml.)	Motility index†	Abnormal forms (%)
1	14	3·5	53
	35	3	48
2	75	3·5	44
	94	0·5	31
3	124	4	9
	180	3·5	31
4	86	4	82
	141	3	46
5	135	1	24
	357	3	34
6	82	0	—
	18	3	32
	71	0·5	48
7	75	0·5	32
	258	0·5	57
	238	3	16

* Swyer, unpublished.
† Emmens (1947).

subfertile patients over 12 weeks with 10–14 mg. daily of 'Ephynal' (Roche Products Ltd.). In twenty-nine patients the seminal variations were entirely within normal limits; in six there was some improvement and in seven some deterioration. In Jackson's (1948) series of fifty subfertile men treated for periods of 3 weeks to 2 years with 'Fertilol' (Vitamins Ltd.), 'Viteolin' (Glaxo Laboratories Ltd.) or 'Ephynal' capsules in similar dosage to that employed by Davidson, seminal examinations before and after treatment were available in thirty-six cases (the number of analyses ranging from two to twenty-eight per patient). Improvement was shown in eleven cases, deterioration in five and no change in twenty. The results, therefore, of Jackson and of Davidson are comparable, and perhaps different from those of Warren. Since the last investigator used from four to six times the dose of the other two, it would seem that the question of adequacy of treatment might be invoked, and that further, and preferably controlled, investigation would be desirable.

Vitamin E has, of course, been used far more widely in female than in male fertility, chiefly in connexion with the treatment and prevention of abortion. A considerable literature on this subject exists, and since its value appears to have been both accepted and rejected in equally uncritical fashion, one or two observations pertinent to a reasoned evaluation might be admissible. Bacharach (1940), for example, has taken the results of treatment with vitamin E, obtained by Vogt-Möller (1931, 1933, 1936) and by Watson & Tew (1935), of cases of repeated abortion and compared them with the expected delivery rates for similar but untreated patients, based on a slight modification of the findings of Malpas (1938). He concluded that the chances of the differences between the published results of treatment in cases with two, three and four previous abortions and the expected results with untreated cases being exceeded on the basis of random variations were 1 in 200, 1 in 10^{10} and 1 in 10^{40}, respectively. Either the observations reported by the two groups of workers are completely false or else there would appear to be overwhelming evidence in favour of the therapeutic efficacy of vitamin E in habitual abortion.

Table 4. *Expected rates of success in pregnancies following abortion sequences in untreated and vitamin E-treated patients, compared with the figures for the latter group collected by Bacharach* (1940)

	Success in next pregnancy		
		Patients treated with vitamin E	
Previous abortions (no.)	Untreated patients (%)*	Bacharach's figures (%)	Theoretical figures (%)
0	90	—	90·4
1	80	—	83·9
2	62	75	81·5
3	27	73	79
4	6	79	76

* Values derived from findings of Malpas (1938), see this page.

The matter may also be considered from a slightly different point of view. Again accepting Malpas's figures (though it might reasonably be pointed out that these have been neither confirmed nor denied by other observers), one may state that, about 10 % of primigravidae will abort; after one abortion 20 % of women will abort in their next pregnancy; after two abortions 38 %; after three, 73 %, and after four, 94 % will abort in their next pregnancy. It is easy to calculate that out of 10,000 primigravidae, 1000 will have one abortion, 200 two, 76 three, 56 four and 52·5 will have five abortions, so that it would seem reasonable to suggest that true 'habitual abortion' exists to the extent of 5–5·25/1000 primigravidae. If the further assumption is made that most habitual abortion is due to vitamin E deficiency, and that adequate therapy might be expected to produce success in 75 % of the susceptible cases, we can compare the expected success rates in untreated cases, in treated cases and in the cases the figures for which were collected by Bacharach (1940) (Table 4). It can be seen that the effect of treatment would not be discernible at all in the groups with one or no previous abortions; in the remainder the agreement between Bacharach's collected figures and the theoretical figures is quite striking.

Vitamins C and K. Finally attention may be directed to two papers which deal with the relation of vitamins C and K to abortion. In the report by Javert & Stander (1943) the plasma vitamin C and prothrombin concentrations of patients complaining of threatened, spontaneous and previous abortions are compared with those of normal pregnant women. There were seventy-nine women in the abortion group, fifty controls for vitamin C, and sixty for prothrombin concentrations (Table 5). The other report, that of King (1945), deals with a similar investigation (using different techniques) in eighty-two patients with previous or inevitable abortions and eighteen with threatened abortions, the findings being compared with those in thirty-two normal, non-pregnant

Table 5. *Concentration of vitamin C and prothrombin in the plasma of patients with threatened, spontaneous and habitual abortions and of normal pregnant women (simplified from Javert & Stander,* 1943)

Group	No. of cases	Vitamin C: Mean value (mg./100 ml.)	Vitamin C: Deficient patients (0·5 mg/100 ml. or less) (%)	Prothrombin: Mean value (percentage of normal)	Prothrombin: Deficient patients (70% of normal or less) (%)
Threatened abortion	20	0·46	—	65	—
Spontaneous abortion	37	0·30	—	46	—
Habitual abortion	22	0·36	—	61	—
Total	79	0·35	69	54	72
Control patients, 4–16 weeks pregnant	50* 60†	0·54	50	92	15

* For vitamin C. † For prothrombin.

women. Unfortunately, in neither paper is any indication of the variance given so that proper analysis is impossible; to gain some idea, however, of the significance of the differences between the abortion and the control groups, the χ^2 have been calculated with the following results:

For vitamin C, the figures of Javert & Stander give a χ^2 of 4·2 and those of King of 0·385; for the pooled figures the χ^2 is 0·99. Without arguing the point too much, therefore, it may seriously be doubted whether there is any real difference between the vitamin C levels of the abortion groups and the control groups.

For prothrombin, on the other hand, King's figures give a χ^2 of 7·68 and those of Javert & Stander of 37·5. It would seem then that deficiency of prothrombin is likely to be found in a highly significant number of women with threatened, previous or habitual abortions (see Table 6).

Table 6. *Comparison of figures of Javert & Stander* (1943) *with those of King* (1945) *for the vitamin C and prothrombin content of the plasma of normal pregnant and non-pregnant women and of women with abortion*

	Normal women: Pregnant (Javert & Stander)	Normal women: Non-pregnant (King)	Women with abortion: (Javert & Stander)	Women with abortion: (King)
Mean vitamin C level (mg./100 ml.)	0·54	1·4	0·35	1·0
Percentage of deficient women (vitamin C level 0·5 mg./100 ml. or less)	50	13	69	21
Mean prothrombin time (% of normal)	92	84·5	54	63
Percentage of deficient women (prothrombin time 70% of normal or less)	15	24	72	52
Percentage of women deficient in both vitamin C and prothrombin	—	0	61	15

Conclusions

The principal conclusions which may be drawn from this brief survey of the relation of nutrition to human fertility is that several indications of an interaction may be found, but that well-established clinical observations are few. Well-planned, properly controlled investigations of a number of points could profitably be undertaken, and, if the results so obtained were submitted to critical assessment, facts might take the place of fancy, the true relation eventually being made clear.

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