Nutrition and Female Fertility

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The relation between nutrition and reproduction is of great practical importance both in human medicine and in animal husbandry. A great mass of data has already been accumulated on reproductive phenomena in nutritionally deficient states, but it can be said that progress in analysis of the problem by means of well-controlled experiments in the light of modern knowledge of nutritional science is only now beginning.

The fact that general malnutrition—decreased caloric intake with associated vitamin deficiencies—leads to lowered fertility has long been known. Reproductive disorders (war amenorrhoea, famine amenorrhoea) associated with inanition were studied after the first World War and were encountered in occupied countries during the second World War (Smith, 1947).

I do not intend to deal with the morass of data on lowered fertility in relation to general undernutrition. Much of the work was not critical in the sense that it is not clear how far the effects were due to specific vitamin lack and how far to secondary effects of the latter. I consider it most useful in this short contribution to try, from the point of view of a reproductive physiologist, to indicate possibilities for a scientific analysis of the problem as it affects the female and to attempt to integrate recent work on more specific aspects into the general picture.

Reproductive physiology of the female

It may be helpful first to give the briefest of summaries of modern knowledge of reproductive physiology in the female. Endocrine mechanisms are most prominent in reproductive processes and have tended until recently to hold the stage to the exclusion of neural influences, which, however, are once again receiving attention. The anterior pituitary governs the endocrine system by virtue of its power to secrete a number of trophic hormones which control the growth or function of other endocrine glands (target glands), among them the gonads. The trophic hormones primarily concerned in reproduction are the follicle-stimulating hormone (F.S.H.) which promotes growth of the Graafian follicle and the later stages of egg maturation, the luteinizing hormone (L.H.) which evokes ovulation and the conversion of the follicle into the corpus luteum (a source of progesterone, a hormone necessary for the maintenance of pregnancy), and finally, prolactin or lactogenic hormone, which is not only essential for the initiation of lactation but is now believed to maintain the secretion of progesterone by the corpus luteum. Other endocrine glands more indirectly concerned in reproduction are the adrenal cortex, stimulated by adrenocorticotrophin (A.C.T.H.) and the thyroid which responds to thyrotrophin. The nature of the mechanism regulating the activity of the endocrine mainspring itself, the anterior pituitary, is not yet clear. The hormones produced by the target glands seem to be involved, but such phenomena as the dependence of ovulation in the rabbit upon coitus indicates that there must also be neural or neurohormonal control by pathways not yet fully elucidated.

Effects of nutritional factors on reproduction

We are now in a position to attempt an analysis of some of the main ways in which nutritional factors may influence reproductive processes in the female and so her overall fertility. These possibilities are summarized below:

(1) Effects on anterior-pituitary function (such as those influencing maturation, shedding and nidation of ova; occurrence and timing of oestrous changes; maintenance of pregnancy).

(2) Effects on nervous system (influencing neural control of hypophysis).

(3) Effects on sex-hormone metabolism (influencing hormone levels of body through changes in rate of production or inactivation).

(4) Effects on responsiveness of accessory reproductive tissues to sex hormones.

(5) Effects of ingestion of sex hormones or substances specifically affecting the activity of endocrine glands.

Anterior-pituitary function

The effects of inanition and vitamin deficiencies on anterior-lobe function have been known since the pioneer studies of Evans & Bishop (1922) in the U.S.A. and Marrian & Parkes (1930) in this country. Female rats on a restricted diet show no oestrous cycles; the ovaries, which seem to be more sensitive to inanition than the testes, are hypoplastic and the uterus infantile. That this is due to a decline in the gonadotrophic activity of the hypophysis and not to a decreased responsiveness of the ovary to a normally maintained gonadotrophic stimulation was shown by the fact that the ovaries of such deficient animals respond to injections of gonadotrophic hormones (Marrian & Parkes, 1930). Such effects have been more recently studied by Mulinos & Pomerantz (1940, 1941), who named the condition 'pseudohypophysectomy'. It is not altogether clear whether these effects were due to simple quantitative restriction of an adequate diet or whether deprivation of certain specific dietary factors below minimum levels was involved. It might be that they are more specific than would at first sight appear, since Friedman & Turner (1939) have shown that the gonadotrophic potency of the rabbit pituitary is unaffected by lowering the dietary protein to 2 % for long periods.

The existence of specific effects of certain vitamins on anterior-pituitary function, such as might imply a relationship between the dietary intake of the vitamin and fertility, has never been conclusively demonstrated. The early studies of Evans & Bishop (1922) in which it was found that supplements of yeast would re-establish oestrous cycles in rats in which ovarian function had been abolished by inanition, indicated the importance of adequate intake of B vitamins for normal reproductive function. The possibility that such effects are mediated through the anterior pituitary is indicated by the fact that the atrophied accessory reproductive organs of vitamin B-deficient rats may be stimulated by gonadotrophin injections (Marrian & Parkes, 1930; Moore & Samuels, 1931).

Under this same heading we may briefly consider the best known case of a dietary factor believed to be specifically implicated in reproductive processes, namely, vitamin

E, often called the antisterility vitamin. As is well known, deficiency of vitamin E in the female rat leads to foetal death and abortion. More speculative, in view of the wide occurrence of this vitamin in common foodstuffs, is the view that vitamin E deficiency may be an important cause of habitual abortion in man and in domestic animals, though the evidence adduced by Bacharach (1940) suggesting the effectiveness of vitamin E therapy in habitual abortion should be noted. It has been claimed that vitamin E deficiency causes changes in the morphology and function of the anterior pituitary which might mediate the reproductive disorders accompanying lack of this principle (Singer, 1936; Barrie, 1937), but evidence to the contrary exists, and the whole position, which has been ably discussed by Mason (1944), is conflicting.

Lowered pituitary function due to nutritional deficiencies, manifesting itself in reproductive difficulties, may be of economic importance in cattle. The widespread occurrence of anoestrus among heifers during the winter in this country became manifest during the war years when a policy of breeding in the winter for autumn calving, so as to boost the winter milk supply, was adopted. The condition, which may range from a state in which the ovaries maintain a functional cycle but without overt heat (silent heat) down to a condition of ovarian hypoplasia with no follicular growth, seemed to be associated in its distribution with unfavourable conditions of climate and nutrition. A lowering or imbalance of hypophyseal gonadotrophic function seems likely to be involved, but some decrease in end-organ responsiveness must also be suspected, since field experiments under the aegis of the Agricultural Research Council, in which attempts were made to induce oestrus and ovulation in anoestrous heifers with pregnant mares' serum gonadotrophin, met with but little success. The condition usually clears up when the cattle have access to fresh grass in the spring, which points the need for further research to evaluate the relative importance of nutritional and other seasonal factors in this form of temporary sterility. The relation between nutrition and infertility in cattle has recently been reviewed by Asdell (1949).

Metabolism of sex hormones

Nutritional factors may affect the reproductive system and so influence fertility by their effects on the metabolism of the sex hormones. The nicely fluctuating level of oestrogen in the female body, an essential link in the proper functioning of the reproductive cycle, is the result of a dynamic balance between the rate of production and the rate of disposal by inactivation and excretion. If the latter process is retarded, a condition may arise in which high, unphysiological levels are maintained in the body, thus throwing the reproductive system out of gear.

Earlier indications that the liver is concerned in the inactivation of oestrogens have been ingeniously confirmed by Biskind & Biskind (1942), who demonstrated the relative ineffectiveness of oestrogen pellets implanted in the spleen as compared with pellets implanted into sites where the hormone is not absorbed directly into the portal blood. Vitamins of the B complex seem to be necessary for oestrogen inactivation by the liver because Biskind & Biskind found that the difference in effectiveness of oestrogen pellets implanted in the two sites was largely abolished in vitamin B-deficient rats but was restored when supplements of B vitamins were added to the diet. Further

studies by various investigators (e.g. Segaloff & Segaloff, 1944; Singher, Kensler, Taylor, Rhoads & Unna, 1944) have confirmed the general theory that the livers of vitamin B-deficient animals show a reduced efficiency in inactivation of oestrogen, and indicate the probable importance of aneurin and riboflavin in this connexion, a deficiency of pyridoxin or pantothenate being, apparently, without effect. Moreover, cirrhotic livers produced by diets low in lipotropic factors also exhibit decreased ability to inactivate oestrogens, and the condition can be cured by administration of methionine (Gyorgy, 1948).

It would thus appear that deficiencies of members of the vitamin B complex or lipotropic factors may lead to the establishment of excessive levels of oestrogen which may be the cause of syndromes resulting in sterility. Pathological uterine bleeding and other disturbances of the menstrual cycle, usually considered to be due to excessive oestrogen production by the ovaries, may perhaps in many cases be due to partial lack of specific food factors required by the liver in connexion with the inactivation and excretion of oestrogen (Biskind, 1946).

Responsiveness of target tissues to sex hormones

Recent work has begun to throw light on the role of nutritional factors in the response of reproductive tissues to sex hormones. Apart from the importance of variations in the sensitivity of the ovary itself to pituitary gonadotrophins, about which very little is known at the present time, we have to consider the responsiveness of accessory reproductive organs such as the Fallopian tube and the uterus to oestrogenic stimulation. The reproductive tract, under the influence of oestrogen and progesterone, undergoes changes directed to providing an hospitable *milieu* for a successful encounter between egg and sperm and for the further entertainment and nidation of the fertilized egg. Interference with this mechanism, either because of relative lack of sex hormones or lowered responsiveness on the part of the accessory reproductive organs, would undoubtedly militate against fertility.

An indication of the importance of specific nutritional factors here has been provided by the interesting work of Herz (1945, 1948), who, studying the effect of specific dietary restrictions on the growth response of the oviduct of the chick to oestrogen, found that the response to maximal doses was absent or negligible in chicks maintained on a diet otherwise complete but deficient in folic acid. In the presence of deficiencies of riboflavin, pyridoxin or pantothenic acid the response was unimpaired. The responsiveness of the oviduct could be restored by addition to the deficient diet of amounts of the order of 20 μg. daily of folic acid.

We seem here to be dealing with a specific nutritional factor necessary for end-organ responsiveness to female sex hormones rather than to any more generalized effect such as, for instance, acceleration of the rate of oestrogen inactivation, since administration of oestrogen to folic acid-deficient chicks evoked the lipaemia which is so characteristic a concomitant of oestrogen administration in the fowl.

The question, of course, arises whether these interesting phenomena have any importance in the mammal. In experiments on monkeys, one of the few mammals known to require exogenous folic acid, Herz (1948) obtained some evidence that in

folic acid deficiency tissues under oestrogenic control, such as the sexual skin, failed to respond to exogenous oestrogen. In addition to confirming the work on chicks, Dorfman (1948) found that in spayed rats, rendered folic acid-deficient by sulphasuxidine, vaginal cornification in response to oestrogen only occurred after administration of folic acid.

This work may thus open up a new and important field of investigation of the relationship between specific dietary factors, of which folic acid seems likely to be of outstanding importance, and the response of the epithelium of the reproductive tract to oestrogen, which would have an obvious and important bearing on fertility. It is by means of researches of this character, made possible by the isolation and availability of members of the vitamin B complex in crystalline form, together with modern means of placing animals in a state of deficiency in respect to one factor only, that real progress in reaching an insight into the intriguing mystery of the vitamin-hormone relationship (a problem no less baffling than the hormone-enzyme relationship with which it is undoubtedly linked) can be expected. Studies of the relation between dietary factors and (*a*) pituitary function and (*b*) sex hormone metabolism should prove enlightening in this connexion.

Sex hormones and goitrogens in the diet

The undoubted fact that the level of sex hormones in the ruminant body may be materially affected by exogenous hormone in the diet was first demonstrated by the studies of Bennetts and his collaborators (Bennetts, 1944; Bennetts, Underwood & Shier, 1946) on sheep grazing on subterranean clover in Western Australia. Ewes on these pastures showed impaired fertility and, particularly striking in wethers (castrated males), there were morphological changes in the urogenital tract indicative of excessive body levels of oestrogen. Eventually (Curnow, Robinson & Underwood, 1948), the implication of oestrogen in these phenomena was put beyond doubt by the chemical extraction of oestrogen from the clover, and an attempt is now being made to isolate and identify the substance concerned.

These striking findings led a group of us at Shinfield, in collaboration with workers at the Courtauld Institute of Biochemistry, Middlesex Hospital, to examine samples of herbage from English pastures for oestrogenic activity, primarily in connexion with the possible involvement of dietary oestrogen in the well-known galactopoietic effects of spring grass (Bartlett, Folley, Rowland, Curnow & Simpson, 1948). In these preliminary studies we have detected appreciable amounts of oestrogenic activity in some samples of rapidly growing herbage, but how far the presence of oestrogen in English pastures at certain times of the year may affect the fertility of stock grazing them remains for future work to demonstrate. As the Australian workers have shown, there is no doubt that excessive intakes of oestrogen can materially reduce fertility in livestock. On the other hand, what we know of the reciprocal relation between the hypophysis and gonads indicates the converse possibility that moderate intakes in the spring grass following a period of anoestrus due to winter conditions might well evoke a reactivation of the anterior pituitary leading to the resumption of oestrous cycles. The possibility that goitrogens, known to be present in *Brassicas* (Chesney, Clawson

& Webster, 1928), may adversely affect the fertility of stock receiving heavy supplements of such greenstuffs as kale, through depression of thyroid function, must also not be forgotten.

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Nutrition and Viable Young

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In its widest sense the word 'fertility' covers the ability of the species to reproduce itself. In the strictest sense it applies to the production by the gonads of healthy zygotes capable of cross-fertilization and production of fertilized ova which can fructify to produce at birth or hatching healthy young of the species. It is clear, therefore, that the strictest sense is the narrower but the primary and more important meaning of the word. From the scientific, the medical and the sociological aspects the wider meaning covering the eventualities during life in the uterus or in the egg is, however, needful of consideration, if only because the life of the fertilized ovum lends itself to study by several different techniques and also is the ultimate object of fertility and reproduction.

Malnutrition in civilian populations

There is considerable evidence that, under conditions of deprivation such as occurred in Europe during the last war, there is both a depression in the birth rate, in the average birth weight, an increase in prematurity, an increase in the abortion rate and a decrease