gesting that there is increased noradrenergic turnover; and cortisol secretion in many depressed patients is not suppressible by dexamethasone, reflecting abnormal activation of the hypothalamic pituitary adrenal axis.⁴ Excessive cortisol production might itself affect immune function, since lymphocytes carry adrenergic and cholinergic receptors, making them directly susceptible to altered neuroendocrine function.⁵ Plasma concentrations of prostaglandins E₁ and E₂ are also increased in depressed patients, and these substances affect immune reactions indirectly by their effects on the hypothalamic control of adrenal function and more directly by their actions on antigen presenting cells.⁶ Those who attribute depressive illnesses and schizophrenia to autoimmune mechanisms might also expect abnormalities in conventional immune functions.^{7 8}

Most studies of the immune responses of depressed patients have analysed the relative and absolute numbers of blood lymphocyte populations. Lymphocyte function has also been tested by measuring the in vitro proliferative responses of T cells to concanavalin A and phytohaemagglutinin and of B cells to pokeweed mitogen. Assays of humoral immunity have been based almost exclusively on determining serum immunoglobulin concentrations. The initial reports claimed that in vitro responsiveness to mitogens was reduced in depressed patients.⁹ But the same group subsequently found normal in vitro responses to mitogens but a mild T lymphopenia in depressed patients not needing admission to hospital.¹⁰ They inferred that impaired immunity was confined to patients with severe illness, but the differences between patients and controls were not compelling, particularly given the wide variation in T cell counts even among controls.

More tellingly, others found that the lymphocyte responses of 27 patients with different depressive illnesses were the same before treatment as those in 13 normal controls.¹¹ After treatment with tricyclic antidepressants, lithium, or electroconvulsive therapy in vitro responses to phytohaemagglutinin and concanavalin A were reduced, emphasising the need to take treatment into account. These results suggest that altered lymphocyte function is not related to the pathogenesis of depression. A more detailed analysis of lymphocyte populations using monoclonal antibodies showed no differences between a few depressed patients and controls.⁶ These workers found impaired in vitro responses to mitogen stimulation, which they attributed to raised plasma prostaglandin concentrations, but their studies were limited and need further analysis.

The evidence for defective humoral immunity in depressed patients is also fragmentary. Reduced plasma IgM concentrations were found in few of the 85 patients admitted to a psychiatric unit; the reduction was also noted in six patients with depressive illnesses.¹² In contrast, the pattern of serum and cerebrospinal fluid immunoglobulins was essentially normal in a group of patients with psychiatric diseases which included seven patients with depression.¹³ There is a dearth of information about specific antibody responses in depressed patients.

Hence little suggests that immune reactions are appreciably altered in depressive illnesses. Moreover, few studies have taken into account the many factors such as treatment, diet, and lifestyle that influence immune response. Even if one were to accept that depressive illnesses are associated with perturbed lymphocyte responses, there is sparse evidence that the changes matter. For example, there is little indication that specific antimicrobial immunity is depressed by depressive illnesses. Some data, however, suggest that an inextricable mixture of stress and depression predisposes to disorders with

an immunological basis – for example, emotional stress may precede the onset of rheumatoid arthritis.¹⁴ Nevertheless, it would be wrong to assume that impaired immunity secondary to depressive illness must initiate such diseases, even if the epidemiological evidence for such associations is strong.

Those who believe that altered immune reactions predispose to depressive illnesses or are an important consequence of such disorders must analyse the responses more closely linked to relevant host defences. Furthermore, they must take concomitant treatment into account.^{6 11} The anti-inflammatory effects of antidepressants might be related to their therapeutic efficacy, but it has still to be shown that these effects are more than a pharmacological irrelevance.¹⁵

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- Stein M, Keller SE, Schieffer SJ. Stress and immunomodulation: the role of depression and neuroendocrine function. *J Immunol* 1985;135:827-33.
- Schieffer SJ, Keller SE, Camerino M, Thornton JC, Stein M. Suppression of lymphocyte stimulation following bereavement. *JAMA* 1983;250:374-7.
- Glaser R, Kiecolt-Glaser JK, Stout JC, Tarr KL, Speicher CE, Holliday JE. Stress-related impairments in cellular immunity. *Psychiatry Res* 1985;16:233-9.
- Rubin AL, Price LH, Charney DS, Heninger GR. Noradrenergic function and the cortisol response to dexamethasone in depression. *Psychiatry Res* 1984;15:5-15.
- Pochet R, Delespessis G, Gauseet PW, Collet H. Distribution of beta-adrenergic receptors on human lymphocyte sub-populations. *Clin Exp Immunol* 1979;38:578-84.
- Calabrese JR, Skwerer RG, Barna B, et al. Depression, immunocompetence, and prostaglandins of the E series. *Psychiatry Res* 1985;27:41-7.
- Pandey RS, Gupta AK, Chaturvedi UC. Autoimmune model of schizophrenia with special reference to antibrain antibodies. *Biol Psychiatry* 1981;16:1123-36.
- Knight JG. Dopamine-receptor-stimulating autoantibodies: A possible cause of schizophrenia. *Lancet* 1982;ii:1073-5.
- Schieffer SJ, Keller SE, Meyerson AT, Raskin MJ, Davis KL, Stein M. Lymphocyte function in major depressive disorder. *Arch Gen Psychiatry* 1984;41:484-6.
- Schieffer SJ, Keller SE, Siris SG, Davis KL, Stein M. Depression and immunity: lymphocyte function in ambulatory depressed patients, hospitalized schizophrenic patients, and patients hospitalized for herniorrhaphy. *Arch Gen Psychiatry* 1985;42:129-33.
- Albrecht J, Helderma JH, Schlessler MA, Rush AJ. A controlled study of cellular immune function in affective disorders before and during somatic therapy. *Psychiatry Res* 1985;15:185-93.
- DeLisi LE, King AC, Targum S. Serum immunoglobulin concentrations in patients admitted to an acute psychiatric in-patient service. *Br J Psychiatry* 1984;145:661-6.
- Roos RP, David K, Meltzer HY. Immunoglobulin studies in patients with psychiatric diseases. *Arch Gen Psychiatry* 1985;42:124-8.
- Baker GHB, Brewerton DA. Rheumatoid arthritis: a psychiatric assessment. *Br Med J* 1981;282:20.
- Hong SL, Carty T, Deykin D. Tranylcypromine and 15-hydroperoxyarachidonate affect arachidonic acid release in addition to inhibition of prostacyclin synthesis in calf aortic endothelial cells. *J Biol Chem* 1980;255:9538-40.

Dietary supplementation in pregnancy

Give me neither poverty nor riches, feed me with food
convenient for me.

PROVERBS xxx, 8

The quality of diet has long been known to affect the fetal condition, a better maternal diet being associated with better condition of the offspring.¹ Extremes of diet, such as those in the Dutch famine in the second world war or associated with obesity,² are well recognised as adversely affecting the outcome of pregnancy, but marginal imbalances are less well understood. In underdeveloped nations with their immense problems of malnutrition the benefits of supplementation may be dramatic,³ but in affluent Western society its value is less certain.

Investigations of the effects of additional calories or a high protein diet during pregnancy have given conflicting results. A New York study of a poor black urban population suggested marginal benefits from balanced supplementation,

whereas a protein rich diet was associated with an increased incidence of premature deliveries, babies with low birth weights, and neonatal deaths.⁴ The Birmingham study of Asian mothers showed no enhancement of intrauterine growth with balanced supplementation.⁵

Prophylactic treatment with iron in pregnancy was introduced against a background of common chronic iron deficiency and is widely accepted. Chronic iron deficiency is now, however, relatively rare in Western Europe, presumably because of improved nutrition, better spacing of pregnancies, and reduced family size. Unnecessary iron supplementation could be harmful, and minor side effects are common. The best approach would appear to be to prescribe only to those women with evidence of deficiency.⁶

Low folate concentrations seem to be related to a poor outcome of pregnancy,⁷ but controversy continues about their relevance to neural tube defects. The case has not been proved, but the evidence is sufficiently strong to have raised considerable opposition to the randomised controlled Medical Research Council trial currently being undertaken.⁸⁻¹⁰ Supplements starting before or very early in pregnancy may be justified in those with a history of neural tube defects or in circumstances where there is an increased demand, such as multiple pregnancy.

Less controversial is the need for supplementation with calcium¹¹ and vitamin D^{12,13} in population groups known to be vulnerable and in countries in which these deficiencies are common.

The development of new assays has led to a surge of interest in the part played by trace elements and minerals. In humans little is known of the role of selenium, chromium, aluminium, molybdenum, and manganese in relation to pregnancy, though recent work has reported on magnesium.¹⁴ Inadvertent exposure in pregnancy to lead and to mercury has been shown to produce mental retardation¹⁵ and cerebral palsy¹⁶ respectively in infants. This should serve to remind us of the potential problems of excesses as well as deficiencies.

Zinc is a current focus of interest and compounds have been licensed and promoted for pregnancy supplementation. Both animal and human studies have related maternal zinc deficiency to poor fetal outcome in the form of an increased incidence of abortions, intrauterine growth retardation, and stillbirths¹⁷⁻¹⁹ and a variety of congenital abnormalities including neural tube defects.^{20,21} Poor maternal performance in pregnancy and an increased complication rate have also been shown.¹⁹ Again, however, a controversy has developed in that blood zinc concentrations previously used to detect the deficiency state have now been shown to be unreliable,²² and assessment is further confused by the haemodynamic changes in pregnancy.²³ More representative tissue sampling, such as in maternal leucocytes,^{18,24} does, however, show that zinc deficiency is related to small for dates fetuses. Supplementation appears to be beneficial in correcting existing deficiencies,^{25,26} but the specialised nature of the assay makes zinc deficiency difficult to define. Studies to date are few; more definitive work is certainly needed here before widespread introduction of supplementation.

The heart of the problem is that, while the limitations of diagnosing deficiency states in daily practice are clearly recognised, routine supplementation must be considered with caution. Many preparations are safe in pregnancy, but the potential dangers of excess use of others have been seen with vitamin A²⁷ and vitamin C.²⁸ Furthermore, supplementation with one nutrient may, by competitive interaction,

prevent the absorption of another.²⁹ Research has concentrated on correlating fetal outcome with maternal nutritional status and deficiency rather than studying the conceptus. Advancing technology should make it possible to assess the fetus or placenta directly.

In view of the obvious difficulties in diagnosing and treating specific dietary deficiencies in pregnancy, the best approach in a relatively affluent Western society must surely be to concentrate more effort on dietary education. A few health authorities are now taking active steps to institute preconception counselling, but all doctors and other health care workers have some responsibility in this respect. In the final analysis, the mother also should accept her responsibility towards the unborn child.

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- Burke BS, Beal VA, Kirkwood SB, Stuart HC. The influence of nutrition upon the condition of the infant at birth. *J Nutr* 1943;26:569-83.
- Tracy TA, Miller GL. Obstetric problems of the massively obese. *Obstet Gynecol* 1969;33:204-7.
- Habicht JP, Yarborough C, Lehtig A, Klein RE. Relation of maternal supplementary feeding during pregnancy to birthweight and other sociobiological factors. In: Winick M, ed. *Proceedings of the symposium on Nutrition and Fetal Development*. New York: John Wiley and Sons, 1974;127-46.
- Rush D, Stein Z, Susser M. A randomised controlled trial of prenatal supplementation in New York city. *Pediatrics* 1980;65:683-97.
- Viegas OAC, Scott PH, Cole TJ, Mansfield HN, Wharton P, Wharton BA. Dietary protein energy supplementation of pregnant Asian mothers at Sorrento, Birmingham. I: unselective during second and third trimesters. *Br Med J* 1982;285:589-92.
- Lind T. Iron supplementation during pregnancy. In: Campbell DM, Gillmer MDG, eds. *Nutrition in Pregnancy. Proceedings of the Tenth Study Group of the Royal College of Obstetricians and Gynaecologists*. London: Royal College of Obstetricians and Gynaecologists 1983:181-91.
- Hibbard BM. Folate and the fetus. *S Afr Med J* 1975;49:1223-6.
- Smithells RW, Sheppard S, Schorah CJ. Vitamin deficiencies and neural tube defects. *Arch Dis Child* 1976;51:944-50.
- Smithells RW, Sheppard S, Schorah CJ, et al. Possible prevention of neural tube defects by preconceptual vitamin supplementation. *Lancet* 1980;ii:339-40.
- Laurence KM, James N, Miller MH, Tenant GB, Campbell H. Double-blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural-tube defects. *Br Med J* 1981;282:1509-11.
- Raman L, Rajalakshmi K, Krishnamachari K, Sastry JG. Effects of calcium supplementation to undernourished mothers during pregnancy on the bone density of neonates. *Am J Clin Nutr* 1978;31:466-9.
- Brooke OG, Brown IRF, Bone CDM, et al. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *Br Med J* 1980;280:751-4.
- Brooke OG, Butters F, Wood C. Intrauterine vitamin D nutrition and postnatal growth in Asian infants. *Br Med J* 1981;283:1024.
- Sheldon WL, Aspillaga MO, Smith PA, Lind T. The effect of oral iron supplementation on zinc and magnesium levels during pregnancy. *Br J Obstet Gynaecol* 1985;92:892-8.
- Moore MR, Meridith PA, Goldberg A. A retrospective analysis of blood lead in mentally retarded children. *Lancet* 1977;ii:717-8.
- Amin-Zaki L, Majeed MA, Elhassani SB, Clarkson TW, Greenwood MR, Doherty RA. Prenatal mercury poisoning. Clinical observations over five years. *Am J Dis Child* 1979;133:172-7.
- Hurley LS, Mutch PB. Prenatal and postnatal development after transitory gestational zinc deficiency in rats. *J Nutr* 1973;103:649-56.
- Meadows NJ, Ruse W, Smith M, et al. Zinc and small babies. *Lancet* 1981;ii:1135-7.
- Jameson S. Effects of zinc deficiency in human reproduction. *Acta Med Scand* 1976;197 (Suppl 593):3-89.
- Baumh PK, Russel M, Bates G, Milford Ward A. Maternal zinc status: a determination of central nervous system malformation. *Br J Obstet Gynaecol* 1984;91:788-90.
- Soltan MH, Jenkins DM. Maternal and fetal plasma zinc concentrations and fetal abnormality. *Br J Obstet Gynaecol* 1982;89:56-8.
- Golub MS, Gerschwin ME, Hurley LS, Baly DL, Hendrickx AG. Studies of marginal zinc deprivation in rhesus monkeys. I: Influence on pregnant dams. *Am J Clin Nutr* 1984;39:265-80.
- Giroux E, Schechter PJ, Schon N. Diminished albumin binding of zinc in serum of pregnant women. *Clin Sci* 1976;51:545-9.
- Simmer K, Thompson RPH. Maternal zinc and intrauterine growth retardation. *Clin Sci* 1985;68:395-9.
- Jameson S. Zinc nutrition in human pregnancy. In: Prasad AS, Cauder AO, Brewer GJ, Aggett P, eds. *Zinc deficiency in human subjects*. New York: Alan R Liss Inc, 1983:53-69.
- Brenton DP, Jackson MJ, Young A. Two pregnancies in a patient with acrodermatitis enteropathica treated with zinc sulphate. *Lancet* 1981;ii:500-2.
- Berhardt IR, Dorsey DJ. Hypervitaminosis A and congenital anomalies in a human subject. *Obstet Gynecol* 1974;43:750-5.
- Cochrane WA. Overnutrition in prenatal and neonatal life: A problem? *Can Med Assoc J* 1965;93:893-9.
- Milne DB, Canfield WK, Mahalko JR, Sandstead HH. Effect of oral folic acid supplements on zinc, copper and iron absorption and excretion. *Am J Clin Nutr* 1984;39:353-9.