Current concepts in medicine

Dietary linoleic acid, immune inhibition and disease

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Summary
Review of the evidence available in published literature supports a radical change in viewpoint with respect to disease in countries where maize is the predominant dietary component. In these countries, the pattern of disease is largely determined by a change in immune profile caused by metabolites of dietary linoleic acid. High intake of linoleic acid in a diet deficient in other polyunsaturated fatty acids and in riboflavin results in high tissue production of prostaglandin E2, which in turn causes inhibition of the proliferation and cytokine production of Th1 cells, mediators of cellular immunity. Tuberculosis, measles, hepatoma, secondary infection in HIV and kwashiorkor are all favoured by this reduction in cellular immunity. Diet-associated inhibition of the Th1 subset is a major contributor to the high prevalence of these diseases found in areas of sub-Saharan Africa where maize is the staple.

Keywords: maize; linoleic acid; prostaglandin E2; cellular immunity; kwashiorkor; diet

Tuberculosis, measles, hepatoma, secondary infection in HIV, and kwashiorkor are all favoured by a reduction in cellular immunity. For example, the prevalence of infection with the tubercle bacillus is reported as 34% in Africa and 28% in Western Europe. Yet expected active tuberculosis for 1990 was 220/100 000 for Africa but only 31/100 000 for Europe and other Western countries.[1] A probable 11 300/100 000 of the population of Transkei, South Africa, had active tuberculosis in 1977.[2] The incidence of active tuberculosis is less a function of prevalence of infection with the bacillus, and more a function of host resistance. High prevalences of tuberculosis have in the past been blamed on social deprivation and dietary deficiency but the variation in the rate of incidence of the disease in different countries is difficult to blame entirely on these factors. For example, the annual notification rate per 100 000 in South Africa is 170 where the GNP is $2740; in Chad, where the GNP is $177, the notification rate is 30 per 100 000.

HIV infection in sub-Saharan Africa has a higher rate of progression to AIDS or to death[3] than in developed countries. It has also been suggested that there is a higher risk of seroconversion after exposure.[4] Several reasons have been suggested to explain its rapid heterosexual spread, including poverty, ignorance, the high rate of sexually transmitted disease (STD), cultural practices,[5] and higher immune activation,[4] but there are several other possible factors. For example, a seasonal pattern was reported in Uganda,[6] which suggests an environmental influence on either the contracting of the disease or on its progression. Similarly, STDs, repeated pregnancies, and immune activation[7] have been blamed for the more rapid progression of HIV to AIDS and to death, with tuberculosis as the most common opportunistic infection.[8] There is so far inadequate evidence to lay the blame for the very different course of the disease in Africa fully on any or all of these factors.

Kwashiorkor is a disease of children in areas where maize is the main dietary component, and it has been suggested that dietary deficiencies are the source of the problem. Sepsis is a frequent terminal event, and there is poor resistance to diseases such as tuberculosis and measles. Measles in Africa does not follow the relatively benign course that occurs in western countries. The disease and its complications are very severe, and are significant contributors to childhood mortality. It is frequently associated with malnutrition, particularly kwashiorkor.

In all these diseases, general factors with undefined mechanisms have been blamed. This paper puts forward the concept of a specific pathological mechanism related to a relative excess of dietary linoleic acid, as a major factor in the incidence and progression of these diseases.

Methods

The relevant literature was found by a review of appropriate journals and literature, Medline searches, and cross-references, and a hypothesis formulated on the basis of published evidence.

Results

Maize is a high yield crop which grows easily in relatively poor soils, and whose use has been spreading up through Africa for over a century, starting from South Africa where it has been the major dietary constituent for most of this century. It contains 5–6% unsaturated fatty acids, the predominant fat being linoleic acid. It is almost the sole provider of calories in some communities in East, Central and Southern Africa and is increasingly used now in West Africa. The main disease caused by vitamin deficiency in communities who are heavily dependent on maize, is pellagra, but ariboflavinosis also occurs.

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Figure 1 Diet and PGE2 production
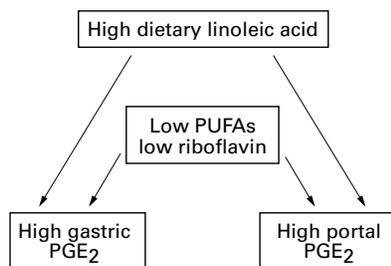

Figure 2 PGE2 and tuberculosis

Figure 3 PGE2, HIV, and AIDS

HIGH LINOLEIC ACID CAUSES HIGH PROSTAGLANDIN E2 PRODUCTION

Linoleic acid is a precursor of prostaglandin E2 (PGE2). High dietary linoleic acid leads to high intragastric PGE2,[9] and, by implication, high PGE2 levels in the portal vein (figure 1). Symptoms suggestive of a high level of gastric PGE2 have been reported in a community whose main diet is maize.[10] A volunteer study showed higher urinary PGE2 levels in volunteers on a high linoleic acid diet than in controls.[11] Salivary gland and gingival PGE2 production is high when linoleic acid intake is high.[12] Plasma PGE2 in rats was higher in the group fed a diet rich in linoleic acid than in other groups.[13]

Dietary fat intake is reflected in the composition of plasma and body adipose tissue.[14] Thus, diet has a long-term effect on the availability of linoleic acid, and on plasma levels of linoleate and its metabolites. High levels of production of PGE2 is further enhanced by an absence of other polyunsaturated fatty acids (PUFAs) in the diet, such as fish oils, which contain eicosapentaenoic acid and docosahexaenoic acid, and which inhibit the conversion of linoleic acid to PGE2.[15] Isomeric PUFAs in hydrogenated foods such as margarine, may also competitively inhibit utilisation of natural PUFAs.

RIBOFLAVIN DEFICIENCY ENHANCES HIGH PGE2 PRODUCTION

Riboflavin deficiency favours the conversion of linoleic acid to PGE2. Riboflavin provides the sulphydryl group for glutathione production, and riboflavin deficiency thus results in glutathione deficiency.[16] Glutathione exerts an inhibitory regulatory influence on prostaglandin synthesis[17] and, in its absence, PGE2 production rises.[18]

A diet high in linoleic acid, low in other polyunsaturated fatty acids and low in vitamins, including riboflavin, is characteristic of the areas of Africa where tuberculosis, HIV, measles and kwashiorkor are rife.
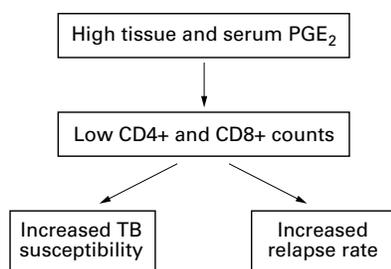
PGE2 DEPRESSES CELLULAR IMMUNITY

The Th1 subset of T-helper lymphocytes mediate delayed-type hypersensitivity reactions. They produce interferon-gamma (IFN-gamma), interleukin-2 (IL-2), and tumour necrosis factor-beta. They are quite distinct from the Th2 subset, which mediate humoral immune response.

PGE2 depresses cellular immunity associated with the Th1 subset of T cells. IL-2 and IFN-gamma producing ability[19] are reduced, this effect being exerted at the level of priming of the naive T cell.[20] Where there is uncontrolled production of PGE2, there will be uncontrolled and inappropriate depression of cellular immunity, and increased susceptibility to infection. An illustration of this is the depression of cellular immunity which follows haemorrhage and is inhibited by ibuprofen,[21] an inhibitor of prostaglandin production.

EXCESSIVE LINOLEIC ACID DEPRESSES CELLULAR IMMUNITY

Studies showing that excessive dietary linoleic acid is immunosuppressive, but that concurrent interference with prostaglandin production prevents or reduces depression of cellular immunity,[22] provide some support for this theory. The immune depression of trauma and burns appears to be prostaglandin associated, and can be similarly blocked with *n*-3 PUFAs.[23]

DEPRESSED CELLULAR IMMUNITY AND DISEASE

Tuberculosis

Protection against tubercle infection is primarily mediated by Th1 cells, and when these are inhibited or reduced in number, host defence is compromised (figure 2). Tuberculosis is strongly associated with the diminished type 1 response[24] and depressed CD4+ count characteristic of HIV infection,[25] and has been noted to occur at a higher CD4+ count than most other opportunistic infections.[26] This may be due to the early loss of Th1 immunity reported in HIV infection at a stage when CD4+ counts are near-normal.[27] Multi-drug-resistant tuberculosis is associated with a poor Th1 response.[28]

This leads to the conclusion that dietary immune deficiency of Th1 function increases susceptibility to tuberculosis. Delayed hypersensitivity reactions to tuberculin have been shown to be reduced in malnourished children.[29]

HIV infection

HIV infection is associated with a similar immune depression to that caused by PGE2 (figure 3). There is reduced Th1 subset proliferation and cytokine production. This can take effect before a major drop occurs in total lymphocyte or CD4+ count.[27]

A pre-existing dietary depression of Th1 subset responsiveness will allow a more rapid progression of HIV infection to AIDS, at least partly by encouraging
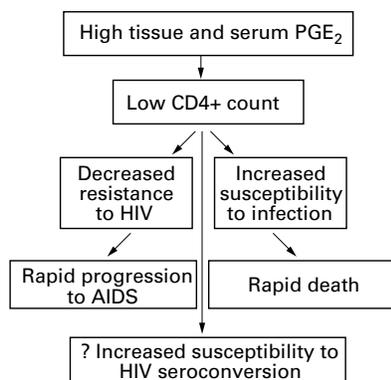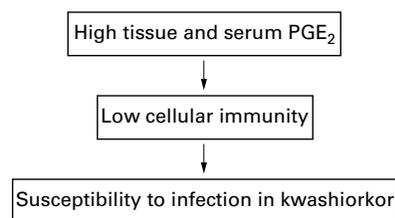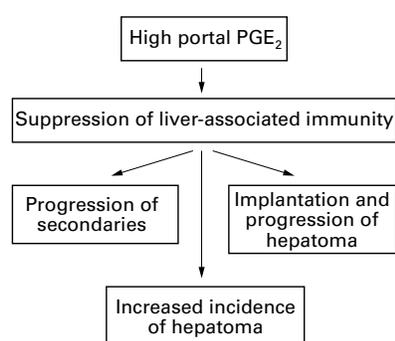
Figure 4 PGE2 and kwashiorkor

Figure 5 PGE2 and hepatoma

AIDS-defining opportunistic infections. There will be susceptibility to life-threatening infection early in HIV infection, before AIDS develops, due to the additive effect of dietary and HIV-related immune depression. A chronically reduced subset 1 response of dietary aetiology may also predispose to HIV sero-conversion on exposure, since natural defence against HIV is most probably vested in the Th1 response.[30]

Kwashiorkor
In kwashiorkor, in addition to the main features of oedema, growth failure, diarrhoea and irritability,[31] cellular immunity is grossly depressed,[32] and affected children are highly susceptible to infectious disease (figure 4).[33] Children with kwashiorkor have decreased T cells in the peripheral blood,[34] with preferential loss of CD4+ cells.[35]

In one study, 25 children who died with kwashiorkor were subjected to autopsy; 21 of them were found to have a 'nutritional thymectomy'.[33] Watts[36] confirmed that thymic atrophy is common in malnutrition; in children under one year old, it was most marked in those with kwashiorkor, in whom the atrophy was very gross. Williams[31] noted that cod liver oil, an excellent source of eicosapentaenoic acid, and therefore an inhibitor of PGE2 production, is an effective treatment for kwashiorkor.

Measles
In severely malnourished children, measles carries a high mortality rate. In the central hospital in Lesotho, five of 28 malnourished children who contracted measles died.[37] Measles virus control is mediated by the Th1 subset of T cells.[38] The reasons for the severe course of the disease may include a low level of virus clearing activity, as well as susceptibility to secondary infection.

Hepatoma
Hepatoma is very common in much of Africa. In rat studies, it has been shown that dietary linoleic acid increases hepatoma growth[39] (figure 5), while indomethacin inhibits it.[40] Similarly, fish oil has been found to inhibit hepatic carcinogenesis,[41] and decrease growth.[42] It is probable that this effect of linoleic acid is mediated through PGE2. Portal PGE2 has also been shown to suppress liver-associated immunity, and promote the formation of hepatic metastases.[43]

Discussion

In the Gambia, evidence has been found of a lifelong change of immune competence brought about by foetal malnutrition.[44] While this may cause an irreversible change, arising from specific episodes of intervention or deficiency, in this article we are talking about a nutritional, and potentially reversible type of immune disturbance. Where population growth, poverty and social disorder coexist, maize with its high yield and ability to grow with little attention or rainfall, is a very valuable crop. However, a diet almost exclusively of maize is seriously flawed, and is a root cause of many of what have been termed 'the diseases of poverty'.

Other diseases, whose principal protection arises from cellular immunity (eg, hydatid disease, malaria, leishmaniasis, syphilis and leprosy), may also be favoured in this situation.

Immune profile shift due to a temporary dietary cause implies the possibility of readjustment of the immune profile by diet. An increase in dietary *n*-3 PUFAs is more efficient than a decrease in *n*-6 acids in reducing PGE2 synthesis.[13 15] This suggests an approach to the problem which may be both effective and achievable.

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