Although lymph-node metastasis would be expected to occur via lymphatic channels, its development is also a sign of systemic metastasis. A coordinated pathway involving angiogenesis in the emergence of metastatic potential is likely,[2,11] and the striking association of high vascular counts with node metastasis provides clinicopathological evidence for this. ER, EGFR, and c-*erb*B-2 are growth factor receptors while p53 is a nuclear protein involved in cell cycle regulation and apoptosis. All have been related to prognosis in or to adverse features of breast cancer. One possible coordinated mechanism would be regulated release of angiogenic factors as a consequence of activation of these receptors or deregulation of differentation. Many new vascular growth factors have been described recently,[18] and antagonism of ones specific to endothelium might provide a new approach to the management of metastasis.

Our findings also suggest that one reason for the success of breast screening is the detection of tumours before a critical number of blood vessels has been induced. In our series, vascular counts in tumours less than 1 cm in diameter and in grade I well-differentiated tumours were in the range for normal breast tissue. If metastasis began at any size screening would not be expected to be of benefit. Vascularisation could explain the low metastasis rate found in smaller screened tumours.[19,20] In animal models, the angiogenic activity of premalignant breast lesions has been suggested to relate to risk of malignancy.[21]

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# Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects

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Ageing is associated with impaired immune responses and increased infection-related morbidity. This study assessed the effect of physiological amounts of vitamins and trace elements on immunocompetence and occurrence of infection-related illness. 96 independently living, healthy elderly individuals were randomly assigned to receive nutrient supplementation or placebo. Nutrient status and immunological variables were assessed at baseline and at 12 months, and the frequency of illness due to infection was ascertained.

Subjects in the supplement group had higher numbers of certain T-cell subsets and natural killer cells, enhanced proliferation response to mitogen, increased interleukin-2 production, and higher antibody response and natural killer cell activity. These subjects were less likely than those in the placebo group to have illness due to infections (mean [SD] 23 [5] *vs* 48 [7] days per year, $p = 0{\cdot}002$).

Supplementation with a modest physiological amount of micronutrients improves immunity and decreases the risk of infection in old age.

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TABLE I—NUTRIENT REFERENCE VALUES FOR HEALTHY INDIVIDUALS

| Vitamin/ nutrient | Index measured | Sample/method | 95% CI* |
|---|---|---|---|
| A | Retinol | S/HPLC | 1·16–4·83 μmol/l |
| β-carotene | β-carotene | S/HPLC | 0·36–1·78 μmol/l |
| B6 | Pyridoxal-5'-phosphate | B/HPLC | 51–127 nmol/l |
| Folates | Pteroyl-glutamic acid | S/RIA | 4–41 nmol/l |
| B12 | Vitamin B12 | S/RIA | 110–680 μmol/l |
| C | Ascorbic and dehydroscorbic acids | P/spectro | 28–116 μmol/l |
| D | $1,25(OH)_2$ vitamin D | S/RRB | 41–136 pmol/l |
| E | α-tocopherol | S/HPLC | 12–48 μmol/l |
| Iron | Ferritin | S/ELISA | 18–280 μg/l (M)<br>12–260 μg/l (F) |
| Zinc | Zinc | S/AAS | 10·3–16·8 μmol/l |
| Selenium | Selenium | S/neutron activation | 1·48–3·63 μmol/l |
| Copper | Copper | S/AAS | 9–27 μmol/l |
| Protein | Albumin | S/bromocresol green | 32–54 g/l |
| | Haemoglobin | B/coulter counter | 132–148 g/l (M)<br>127–143 g/l (F) |

HPLC = high-performance liquid-chromatography, RIA = radioimmunoassay, spectro = spectrophotometry, RRB = radioreceptor binding, ELISA = enzyme-linked immunosorbent assay, AAS = atomic absorption spectrophotometry, S = serum, B = whole blood, P = plasma.
*Based on 38–141 individuals for various tests.

## Introduction

Ageing is generally associated with impaired immune responses[1,2] and increased frequency of infection (especially respiratory disease[3,4]), which is a major cause of illness and the fourth commonest cause of death in elderly people. However, at least 25% of old individuals have immune responses as vigorous as those of young adults.

Nutrition is an important determinant of immunocompetence. Protein-energy malnutrition and deficiencies of various nutrients impair several immune responses, especially cell-mediated immunity,[5-8] and nutritional disorders are common in old age.[9-11] Supplementation with selected nutrients may improve certain aspects of the immune system. However, in previous studies the number of subjects has been small, large pharmacological doses of single nutrient or a few nutrients were used, and the duration of supplementation and follow-up was limited.[12-17] The use of a single nutrient in large doses may lead to secondary alterations in requirements, to malabsorption of other nutrients, and in some instances, to impaired immune responses.[18] For example, Payette and colleagues[19] showed that high dietary intakes of vitamins E and D were associated with decreased activity of interleukin-2 (IL-2). Most importantly, morbidity has not been evaluated systematically.

In this report, the hypothesis tested is that an optimum intake of all essential micronutrients in physiological amounts will result in an improvement in immune responses and reduce the frequency of infection in old age.

## Subjects and methods

Senior citizens identified from the St John's City census were contacted, and those who were apparently healthy and living independently were asked to take part. All individuals approached enrolled in the study. 96 men and women over 65 years of age volunteered for this double-blind placebo-controlled trial, and gave informed consent. They were of English or Irish ancestory and were middle class (family income > Canadian $48 000). None of the subjects had any known chronic or serious illness, and were not taking medications that might have interfered with nutritional status or immunocompetence. They were randomly assigned to receive either placebo or nutrient supplement based on four blocks of 24 random numbers, and they were unaware of the group to which they had been allocated.

The daily oral supplement (patent applied for) contained vitamin A 400 retinol equivalents, β-carotene 16 mg, thiamin 2·2 mg, riboflavin 1·5 mg, niacin 16 mg, vitamin B6 3·0 mg, folate 400 μg, vitamin B12 4·0 μg, vitamin C 80 mg, vitamin D 4 μg, vitamin E 44 mg, iron 16 mg, zinc 14 mg, copper 1·4 mg, selenium 20 μg, iodine 0·2 mg, calcium 200 mg, and magnesium 100 mg. The amounts of various nutrients are similar to the recommended nutrient intakes in Canada and the recommended dietary allowances in the USA with the exception of vitamin E and β-carotene, which were about four times the upper quartile of usual intakes. The placebo contained calcium 200 mg and magnesium 100 mg. The supplement and the placebo appeared identical and were prepared specifically for this study. Subjects, observers, and laboratory personnel were unaware of the nature of the supplement given. Subjects were advised to continue their normal activity and to report any unusual symptoms or changes in appetite or weight. Compliance was verified by interview at fortnightly visits and counting of leftover medication.

To obtain nutrient reference values, fasting blood samples of healthy men and women aged 66–88 years (living in Newfoundland) were evaluated (table I). Each subject had been followed up for 1–3 years after blood nutrient estimation, and the results of only those who had remained healthy were included in the calculation of the normal reference standard. All individuals were white and of upper-middle-to-high socioeconomic status (family income > Canadian$48 000). The distributions of values were approximately normal. Subjects in the randomised trial whose blood nutrient values fell below the 95% confidence limits of these "normal" reference standards were defined as deficient.

Complete blood profile and count was obtained from each subject. Peripheral blood mononuclear cells were separated from heparinised blood by density-gradient centrifugation. Cells were washed and used to count subsets with commercial monoclonal antibodies, and to assess production of IL-2, and natural killer (NK) cell activity.[20-25] Subjects were tested at the start of the study and after 12 months of placebo or supplement. Influenza vaccine was given four weeks before the end of the study and antibody level estimated. For all laboratory tests, the average of three estimations was used in the analysis.

Subjects were asked to contact the principal investigator or his clinical delegate in the event of any illness. Diagnosis of infection was based on clinical features and appropriate laboratory tests; blood counts; radiography of the chest and sinuses; bacterial and fungal cultures of sputum, urine, and blood; C-reactive protein; endotoxin; and erythrocyte sedimentation rate. Subjects with

TABLE II—DEMOGRAPHIC DATA AND NUTRITIONAL STATUS

| Variable | Placebo group | | Supplement group | | Difference between $S_0$ and $S_{12}$ (p) |
|---|---|---|---|---|---|
| | 0 mo ($P_0$) | 12 mo ($P_{12}$) | 0 mo ($S_0$) | 12 mo ($S_{12}$) | |
| *No of subjects* | 48 | 41 | 48 | 45 | .. |
| *Mean age (yr)* | 74 | .. | 75 | .. | .. |
| (range) | (68–84) | | (66–86) | | |
| *M/F* | 21/27 | 17/24 | 20/28 | 18/27 | .. |
| *Nutrient deficiency (%)** | | | | | |
| Vitamin A | 8·3 | 7·3 | 12·5 | 2·2 | 0·05 |
| β-carotene | 12·5 | 9·7 | 16·7 | 0 | 0·017 |
| Vitamin B6 | 10·4 | 9·7 | 16·7 | 4·4 | 0·046 |
| Folic acid | 4·2 | 7·3 | 6·2 | 2·2 | NS |
| Vitamin B12 | 6·2 | 9·7 | 6·2 | 4·4 | NS |
| Vitamin C | 18·7 | 16·6 | 22·9 | 4·4 | 0·008 |
| Vitamin D | 4·2 | 7·3 | 6·25 | 0 | NS |
| Vitamin E | 8·3 | 12·2 | 8·3 | 2 2 | NS |
| Iron | 12·5 | 9·8 | 14·5 | 2·2 | 0·032 |
| Zinc | 14·6 | 14·6 | 16·7 | 4·4 | 0·046 |
| Selenium | 2·1 | 2·4 | 0 | 2·2 | NS |
| Copper | 4·2 | 2·4 | 2·1 | 2·2 | NS |
| Albumin | 8·3 | 12·2 | 10·4 | 8·9 | NS |
| Haemoglobin | 6·2 | 4·9 | 6·2 | 2·2 | NS |

NS = not significant, p > 0·05.
*Deficiency defined as blood concentration below 95% CI

TABLE III—IMMUNOLOGICAL DATA

| Variable | Placebo | | Supplement | | Difference between | |
|---|---|---|---|---|---|---|
| | 0 mo ($P_0$) | 12 mo ($P_{12}$) | 0 mo ($S_0$) | 12 mo ($S_{12}$) | $S_0$ and $S_{12}$ (p) | $P_0 \rightarrow P_{12}$ and $S_0 \rightarrow S_{12}$ (p) |
| *Lymphocyte count (× 10⁹/l)* | 5·6 (0·7) | 4·8 (1·1) | 4·9 (1·3) | 5·3 (1·2) | NS | NS |
| *T cells (%)* | | | | | | |
| CD3 | 56·4 (3·1) | 52·8 (4·2) | 54·6 (3·7) | 66·1 (4·0) | 0·012 | 0·003 |
| CD3/CD25 | 10·1 (1·8) | 10·2 (2·0) | 12·1 (2·1) | 21·4 (2·4) | 0·002 | 0·001 |
| CD4 | 40·4 (3·8) | 42·1 (3·3) | 38·6 (2·9) | 48·9 (2·7) | 0·028 | 0·007 |
| CD4/CD45RA | 21·6 (2·7) | 20·7 (3·2) | 20·8 (2·9) | 16·6 (3·0) | NS | NS |
| CD8 | 19·3 (3·0) | 22·1 (2·7) | 18·6 (3·7) | 21·4 (2·8) | NS | NS |
| *B cells (%)* | 10·2 (2·0) | 9·8 (1·6) | 10·8 (1·1) | 11·2 (1·6) | NS | NS |
| *NK cells (%)* | 8·8 (1·2) | 9·3 (1·6) | 8·1 (0·7) | 12·7 (1·6) | 0·033 | 0·016 |
| *Lymphocyte response to phytohaemagglutinin (cpm)* | 48 125 (8636) | 52 978 (5688) | 44 135 (7231) | 87 601 (9345) | 0·036 | 0·008 |
| *IL-2 (U/ml)* | 4·2 (0·7) | 3·6 (0·8) | 4·7 (1·0) | 12·8 (1·2) | 0·001 | 0·001 |
| *IL-2 receptor (U/μl)* | 3·8 (1·1) | 4·1 (0·8) | 4·3 (0·7) | 8·1 (1·6) | 0·016 | 0·004 |
| *NK cell activity (%)* | 22 (4) | 27 (3) | 25 (4) | 41 (5) | 0·009 | 0·002 |
| *Antibody response to influenza vaccine (log reciprocal)* | ND | 2·1 (0·4)* | ND | 3·2 (0·5)* | .. | .. |

Data shown as mean (SD) ND = not done; NS = not significant, p > 0 05, cpm = counts per min.
*p = 0·043.

infection were treated appropriately with antimicrobial agents and supportive measures. Data on additional illness were collected by personal interviews every 2 weeks throughout the study. Information obtained in these sessions was supported by reports from the family physicians and hospital outpatient clinics.

The number of individuals defined as deficient for each nutrient at 0 and 12 months was compared for each group by the $\chi^2$ or Fisher's exact probability tests. The two groups were compared with respect to mean change in immune responses per individual (unpaired *t* test) and to morbidity and antibiotic use (unpaired Wilcoxon rank-sum test). Results of immune responses were correlated with blood nutrient concentrations by Pearson's coefficient. Statistical tests were conducted on appropriately transformed data when the observed values were not distributed normally.

## Results and discussion

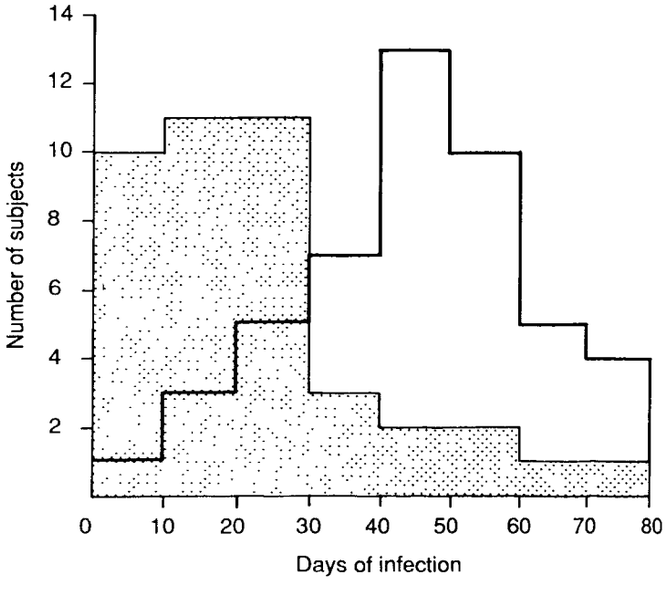
The two groups were similar in age and sex distribution (table II). 7 subjects in the placebo group and 3 in the supplemented group were excluded from the final analyses. 2 placebo subjects died during the trial, 1 of cerebrovascular accident and the other of lung cancer; 5 placebo subjects and 3 supplemented subjects withdrew from the study for personal reasons.

At baseline, prevalence of nutrient deficiency did not differ between the two groups for any of the nutrients tested. There was no significant change in the occurrence of deficiencies over the 12 months in the placebo group. However, there was a statistically significant reduction in deficiencies of vitamin A, β-carotene, vitamin B6, vitamin C, iron, and zinc in the supplemented group (table II).

Although the absolute number of neutrophils or lymphocytes did not change over the study, several immunological responses showed a statistically significant improvement in the supplemented group, including the number of T cells and NK cells, lymphocyte response to phytohaemagglutinin, IL-2 production, IL-2 receptor release, NK cell activity, and antibody response to influenza vaccine (table III). Improvement in immunological responses was greater among subjects who at baseline had shown evidence of nutrient deficiency which was corrected after 12 months of supplement use. There was no significant relation between weight-for-height or midarm circumference and any of the immunological tests in either of the two groups. However, there were significant correlations between serum ferritin and NK cell activity ($r = 0·61$), serum zinc and IL-2 production ($r = 0·69$), serum zinc and NK cell activity ($r = 0·48$), serum vitamin B6 and lymphocyte responses to mitogen ($r = 0·38$), and serum β-carotene and IL-2 production ($r = 0·43$).

Furthermore, infection-related illness was much less frequent in the supplemented group than in the placebo group (mean [SD] 23 [5] *vs* 48 [7] days per year, p = 0·002). This difference was the result of a general reduction in infection, rather than a selective reduction affecting only individuals with prolonged illness (figure). The mean (SD) number of days for which antibiotics were used rather than merely prescribed also differed between the two groups (placebo 32 [5] *vs* supplement 18 [4], p = 0·004).

This study confirms both the prevalence of micronutrient deficiences and an age-associated reduction in immune responses in apparently healthy elderly individuals. The predominant beneficial effect of supplementation on cell-




**Distribution of infection-related morbidity in placebo (open) and supplemented (shaded) groups.**

mediated immune responses in the elderly is similar to that recorded in younger subjects.

Supplementation with modest physiological amounts of essential vitamins and trace elements resulted in a significant improvement in several indices of immunocompetence. It is important to note that large-dose supplements were not used; indeed very large doses of many micronutrients may impair immunity.[6,18,24,25] Every micronutrient seems to have an upper and lower threshold for optimum immune function.[6,25]

The results of this study substantiate the hypothesis that nutritional status is an important determinant of immunocompetence in old age and that an optimum intake of micronutrients is needed for enhanced immune responses in elderly subjects. Such an intervention led to a striking reduction in illness, a finding that is of considerable clinical and public-health importance.

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# SHORT REPORTS

## Adult coronary artery disease probably due to childhood Kawasaki disease

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We have surveyed adult survivors of childhood Kawasaki disease (KD) who had coronary artery disease that could be ascribed to KD. In response to questionnaires sent to cardiologists throughout Japan, 21 patients (17 men, 4 women, aged 20–63 years) with coronary lesions and a definite (2) or suspected (19) history of KD were reported. 5 patients had presented with acute myocardial infarction, 6 previous myocardial infarction, 9 angina pectoris, and 1 dilated cardiomyopathy. 16 patients had obstructions in two or more coronary arteries. 3 had died and 18 were alive with serious sequelae (mitral regurgitation, arrhythmias, congestive heart failure). Childhood KD should be included in the differential diagnosis of coronary artery disease in young adults.

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The most important clinical feature of Kawasaki disease (KD), an acute febrile illness affecting mainly infants and young children,[1] is coronary artery involvement, which may lead to sudden death or ischaemic heart disease.[2,3] We have studied adult survivors of childhood KD who had coronary artery disease probably secondary to KD.

We sent questionnaires and diagnostic guidelines for acute KD (prepared by the Kawasaki Disease Research Committee) to cardiologists in all 354 major hospitals and cardiovascular centres throughout Japan, where coronary angiography is routinely performed. The response rate was 46%. 101 hospitals had no experience of patients who had survived childhood KD. 21 patients with ischaemic heart disease and a definite or suspected history of KD were reported from 18 hospitals. We classified cases as definite