Occasional Survey

LYMPHOMAS AND ANIMAL-PROTEIN CONSUMPTION

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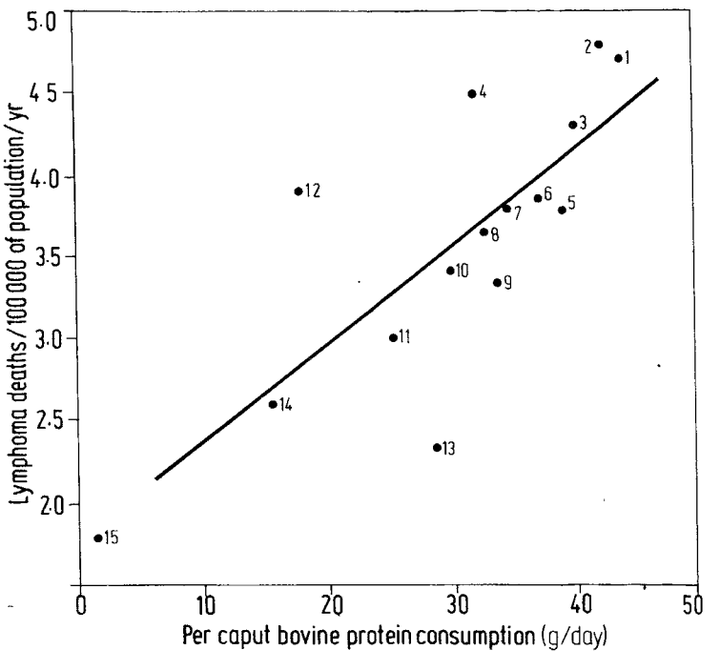
Summary Geographic comparison reveals a positive correlation between consumption of animal protein, particularly bovine protein, and lymphoma mortality. Allied observations suggest that excessive consumption of animal protein may, through antigen absorption and chronic persistent stimulation, impose considerable wear and tear on lymphoid tissue and thereby encourage malignant changes.

INTRODUCTION

HUMAN lymphomas may result from a combination of genetic and environmental factors.[1] Nutrition has hardly received any attention as a possible factor, though two observations suggest that overnutrition, especially of protein, may be a factor in the pathogenesis of lymphomas. Firstly, lymphomas are more common in the upper socioeconomic groups and others with high food and protein intakes.[2] Secondly, protein augmentation of the diet of rats increases the number of lymphomas which they develop.[3] Data on protein consumption in man were, therefore, reviewed in parallel with lymphoma statistics to see whether any relation could be established between the two.

GEOGRAPHIC SURVEY OF PROTEIN CONSUMPTION AND LYMPHOMA DEATHS

Age-standardised death-rates for lymphosarcoma/reticulosarcoma, Hodgkin's disease, and all cancers were calculated from data published by the World Health Organisation (table I).[4] Per caput consumption of the major food protein sources was tabulated from data published by the Organisation for Economic Cooperation and Development (O.E.C.D.) (table II).[5] Linear regression analysis was performed on data from 15 countries for which complete information was available (table III). A highly significant positive correlation was found between deaths from lymphomas and animal protein consumption (r=0·74; P<0·005), with the highest correlation for bovine proteins (r=0·79; P<0·0005) (see accompanying figure). Even when the outlying point for Japan is excluded from regression analysis, a significant correlation remains between bovine-protein consumption and lymphoma deaths (r=0·68; P<0·005). Strong



Geographical correlation between per caput consumption of bovine protein 1955–56, and combined deaths from lymphosarcoma, reticulosarcoma, and Hodgkin's disease for all ages per 100 000 of population per year, 1963–65.

Age-standardised death-rates have been used and are listed in table I. Protein consumption data are given in table II. Numbers are keyed to the countries listed in tables I and II.

TABLE I—MORTALITY DATA

Country	Deaths per 100 000 population per year (all ages 1963–1965)					
	Crude rate*			Age-standardised rate†		
	Lympho/ reticulo sarcoma	Hodgkin's disease	All cancers	Lympho/ reticulo sarcoma	Hodgkin's disease	All cancers
1. New Zealand	3·43	1·68	144	3·11	1·61	128
2. United States	3·66	1·76	152	3·15	1·63	126
3. Canada	2·81	1·48	133	2·77	1·50	127
4. Denmark	3·31	2·39	223	2·44	2·03	154
5. Finland	2·48	1·65	158	2·24	1·53	141
6. Switzerland	2·42	2·24	189	1·89	1·96	135
7. Sweden	3·25	2·18	190	2·15	1·63	115
8. Norway	2·96	1·91	171	2·05	1·59	113
9. Netherlands	1·84	1·88	181	1·56	1·78	146
10. United Kingdom	2·55	1·79	220	1·91	1·49	144
11. Belgium	1·63	2·08	234	1·25	1·76	148
12. Italy	2·26	2·23	159	1·94	1·96	123
13. France	1·39	1·45	204	1·08	1·26	131
14. Yugoslavia	1·61	·99	83	1·62	·98	84
15. Japan	1·18	·51	107	1·24	·55	116

*Calculated from World Health Organisation data.[4]

†Calculated from the crude rate by the method of Doll et al.[31] on the basis of a standard world population.

TABLE II—PROTEIN CONSUMPTION DATA

Country	Per caput protein consumption (g per day 1955–56)*									
	Beef/ dairy	Pork	Poultry/ eggs	Fish	Cereal grains	Pulses, nuts, seeds	Potatoes, starches	Animal protein	Crop protein	Total protein
1. New Zealand	43·8	4·0	5·0	1·9	27·0	1·2	2·3	68·1	34·2	102·2
2. United States	42·2	8·3	11·0	2·2	20·7	3·8	2·1	67·1	32·2	99·2
3. Canada	40·0	6·4	8·9	2·6	22·1	1·8	3·1	60·9	31·0	91·9
4. Denmark	32·0	9·6	3·9	5·5	24·2	·5	5·6	51·3	32·7	83·9
5. Finland	39·1	4·1	2·2	3·5	34·4	1·1	4·8	50·7	41·4	92·2
6. Switzerland	36·9	6·4	3·7	1·2	30·8	2·2	3·4	50·8	41·5	92·3
7. Sweden	34·5	7·1	4·1	7·4	22·9	1·2	4·5	55·1	30·8	85·9
8. Norway	32·3	4·1	2·7	8·8	27·1	1·8	4·9	51·1	36·1	87·2
9. Netherlands	33·9	5·9	3·7	4·0	26·9	1·5	4·2	49·7	36·3	86·0
10. United Kingdom	29·9	5·8	5·6	2·8	27·2	2·8	4·4	52·1	37·7	89·8
11. Belgium	25·2	7·3	5·6	4·9	29·0	1·7	6·9	46·8	41·8	88·6
12. Italy	18·0	2·1	3·4	2·8	41·8	4·4	2·0	28·0	53·2	81·2
13. France	28·8	7·2	5·7	3·7	33·0	2·6	5·9	51·1	47·3	98·4
14. Yugoslavia	15·9	2·9	2·0	·3	55·1	5·6	3·0	22·7	66·3	89·0
15. Japan	1·5	·4	1·4	11·0	33·4	13·5	2·6	15·1	53·2	68·3

*Calculated from data collected by the Organisation of Economic Cooperation and Development.[5]

TABLE III—CORRELATION COEFFICIENTS FOR PER CAPUT PROTEIN CONSUMPTION AND DEATH-RATES

Source	Lymphosarcoma and reticulosarcoma	Hodgkin's disease	Lymphosarcoma, reticulosarcoma, and Hodgkin's disease	All cancers
Dairy/beef	0·70*	0·61†	0·79‡	0·38
Pork	0·26	0·57	0·45	0·54
Poultry/eggs	0·53	0·24	0·50	0·22
Fish	−0·31	−0·33	−0·38	−0·02
Potatoes/starches	−0·46	0·20	−0·25	0·48
Cereal grains	−0·46	−0·38	−0·52	−0·58
Pulses, nuts, seeds	−0·38	−0·78	−0·63	−0·45
All animal protein	0·67*	0·53	0·74*	0·44
All crop protein	−0·60	−0·54	−0·69	−0·56
Total protein	0·48	0·31	0·50	0·12

Correlations based on age-standardised death-rates and protein consumption data in table I and table II.
*$P<0·005$ ‡$P<0·0005$
†$P<0·01$ (One-tailed t test.).

positive correlations were not found for other foods or with cancer in general.

Caution is necessary in drawing conclusions about ætiology from these epidemiological parallels. Nevertheless, other considerations suggest that these associations are probably not fortuitous.

LYMPHOID STIMULATION AND FOOD PROTEIN ABSORPTION

The average intake of protein in many countries is far in excess of the recommended requirements.[6] Excessive consumption of animal protein may be one co-factor in the causation of lymphomas by acting in the following manner. Ingestion of certain proteins results in the absorption of antigenic fragments through the gastrointestinal mucous membrane. This results in chronic stimulation of lymphoid tissue to which these fragments gain access. Whether or not such stimulation alters immunological function, it may act in concert with other factors such as genetic susceptibility and oncogenic viruses to produce malignant change.

Chronic immunological stimulation causes lymphomas in laboratory animals and is believed to cause lymphoid cancers in man.[7] Burkitt's tumour is a human lymphoma in which malaria has been implicated as the immunostimulant co-factor.[8] As mentioned, augmentation of dietary protein (casein) increases the number of lymphomas which develop in rats.[3] In lymphoma-prone mice, moderate protein restriction prevents thymic involution and splenomegaly and enhances cell-mediated immunity and antibody-producing capacity.[9]

The gastrointestinal mucous membrane is only a partial barrier to the absorption of food antigens, and circulating antibody to food protein is commonplace in a healthy population.[10] If the gastrointestinal tract is abnormal, as it is in persons with cœliac disease, antigen absorption and subsequent antibody production are exaggerated.[10 11] This is a telling example of the relation between antigen absorption and lymphomas, since lymphomas are a hundred times more common in those with cœliac disease than in the general population.[12]

Bovine proteins may be especially potent lymphoid stimulants. Ingestion of cow's milk can produce generalised lymphadenopathy, hepatosplenomegaly, and profound adenoid hypertrophy.[13 14] It has been conservatively estimated that more than 100 distinct antigens are released by the normal digestion of cow's milk,[15] which may evoke production of all antibody classes.[16] In patients with cœliac disease and other disorders of the gastrointestinal mucosa, circulating antibody to bovine proteins is more common and is present in larger quantities than antibody to other common food sources.[10 11]

PARALLELS BETWEEN LYMPHOMA AND FOOD CONSUMPTION DATA

Overnutrition and immunostimulation explain several features of lymphomas. People in upper socioeconomic

groups and others subject to increased lymphoma risk tend to be overnourished.[2 17] Hodgkin's disease is six times more common in those taking anti-obesity drugs than in non-users.[18] The increase in the frequency of lymphomas in Japanese people who move to the U.S.A. is probably the result of their adoption of Western dietary habits.[19–21] Consumption of bovine protein is greater in northern Europe, North America, the northern U.S.A., and among upper socioeconomic groups, males, farm residents, small families, and Caucasians.[5 17 22 23] Mortality from lymphoma, especially Hodgkin's disease, is comparatively high in each instance.[2 4 24–27] The association between adenotonsillectomy and Hodgkin's disease may be due to the association of both these conditions with the ingestion of dairy products (geographic correlation for Hodgkin's: $r=0{\cdot}64$; $P<0{\cdot}005$). This is an alternative to the hypothesis that adenotonsillectomy produces Hodgkin's disease via local immunodeficiency.[28] The predilection of non-Hodgkin's lymphoma for the gastrointestinal tract probably results from the fact that this is the prime site of antigen absorption.[29] Although lymphomas are found in association with defective immunity,[7] they predominantly occur in groups whose immunity has been believed to be enhanced by nutritional advantage (upper socioeconomic groups, &c.).[2] This paradox is resolved by the present observations and the knowledge that protein overnutrition depresses immunity.[9]

It must be acknowledged that animal foods are a potential source of infection by oncogenic viruses,[30] and that the ætiology of lymphomas is complex. Nevertheless, the present observations suggest that nutritional factors should be considered and the dietary histories of lymphoma patients examined.

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Medical Education

TOWARDS PARITY FOR THERAPEUTICS IN CLINICAL TEACHING

Two quite different methods of teaching are used in clinical medicine. In one, packages of knowledge, such as books and lectures about diseases and their management, are presented to the students for assimilation. In the other, the student learns how to take a history and examine people and then practises these skills under supervision on actual patients in the care of his teachers. Both methods are needed, and are used in all British medical schools to teach diagnosis; but only the first is widely used to teach clinical pharmacology and therapeutics, because there are too few clinical pharmacologists for "clinical apprenticeship" teaching to be practicable. At present, therefore, students learn very little about treatment from the cases that they see, and that is a great waste of potentially valuable experience. But students could learn from this experience if they knew how to organise it in their minds—that is, if they knew what questions to ask themselves. The accompanying list of questions tries to help them do this. It is arranged in fairly logical sequence to make it easy to use and to remember, like the conventional headings for history-taking and clinical examination.

To all clinical students

QUESTIONS TO ASK YOURSELF ABOUT DRUGS

One of your main chances to learn about drugs occurs while you are doing clinical work. The questions below will help you to learn more systematically from this experience. Ask yourself these questions to assess your knowledge. If you cannot answer them for yourself discuss them with those who are treating the patient.

Look at the treatment sheet at the end of the patient's bed or the outpatient prescription form. Some of the drug names may be unfamiliar. You will need to find out about these.

1. *Name*	For each drug listed, what is the approved or generic name?
2. *Class*	To what class does each drug belong (e.g., diuretic, phenothiazine)?
3. *Aim*	What aim is to be achieved with each drug? What disorder of function is to be corrected, or what symptom relieved?
4. *Observations*	What observations can be made to judge whether the aim has been achieved? When should they be made and by whom?
5. *Route and dosage*	By what route, in what dose, and at what intervals is each drug to be given, and why? In what form(s) does each drug come?
6. *Alternatives*	What other remedies might have been chosen instead of these drugs? Is this drug a good choice (efficacy, safety, cost)?
7. *Duration*	How long should treatment go on, and when and how could a decision be made to stop?
8. *Elimination*	How is the drug eliminated? Will the patient's illness change the usual pattern of distribution and effects of the drug?
9. *Unwanted effects*	What undesirable effects may occur from this drug? Are they acceptable? What is their approximate frequency?
10. *Interactions*	Are there any other drugs which should be avoided while the patient is receiving this treatment? If yes, which are they and why should they be avoided?
11. *Patient's Ideas*	What does the patient believe about the drug? What has he been told about it? And what has he remembered? Does he need additional information?

The use of such a question list has several important advantages: (a) it makes clear to the student that it is his responsi-