Review article

The role of meat in the expression of rheumatoid arthritis

William B. Grant

12 Sir Francis Wyatt Place, Newport News, VA 23606-3660, USA

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Rheumatoid arthritis (RA) is characterized by inflammation of the synovial tissues in the joints. A number of papers related to dietary components that are associated with this inflammation are reviewed. In addition, the ecological approach is used to study the links between diet and RA. Multi-country data for prevalence of RA for females from eight and fifteen countries were compared statistically with components of national dietary supply. Fat from meat and offal for the period 2 years before the prevalence data was found to have the highest statistical association with the prevalence of RA (r^2 0·877, $P<0·001$ for eight countries). The statistical correlations for meat and offal were almost as high as those for their fat. Similar correlations were found for temporal changes in indices of effects of RA in several European countries between 1968 and 1978 as more meat was added to the national diets, although the correlations were higher for meat than for fat. It is hypothesized that meat and offal may be a major factor contributing to the inflammation in RA. In the present short review, the author examines some of the data that associate meat consumption with RA and the possible factors, e.g. fat, Fe and nitrite, which may contribute to the inflammation.

Diet: Fat: Meat: Oxidative stress: Rheumatoid arthritis

Rheumatoid arthritis (RA) is a form of arthritis in which the synovial tissues in the joints become inflamed. The search for the causes of RA has not led to any general agreement on the aetiology of RA (Fox, 1997). While approximately 150 studies have found dietary influences on RA (Panush, 1997; Henderson & Panush, 1999), the level of scientific methodology for most of the studies is such that generally they are not accepted by the medical establishment. Often the studies were performed on a small group of subjects without adequate case–control protocols. However, some studies did meet high scientific standards (for example, see Darlington *et al.* 1986; Kjeldsen-Kragh *et al.* 1991; Kavanagh *et al.* 1995; Kjeldsen-Kragh, 1999). Even then, it appears that diet affects the severity of RA symptoms, rather than its prevalence. The most recent paper in this series, (Kjeldsen-Kragh, 1999) reported the results of a diet that started with fasting followed by a vegan diet for 3·5 months, after which milk, dairy products and gluten-containing foods were introduced one at a time, and again excluded if they exacerbated RA symptoms. While the diet was successful in reducing the symptoms of RA, the reason for the success was not reported.

Fat and meat

Dietary fat has often been implicated in RA symptoms (Cleland, 1991; James & Cleland, 1997). Arachidonic acid, primarily synthesized from linoleic acid, but also found in small amounts in meat, is generally associated with inflammation through production of series 2 prostaglandins (Cleland, 1991; Erasmus, 1993; James & Cleland, 1997). Excess linoleic acid from such sources as soyabeans and sunflower and maize oils (Erasmus, 1993) has been implicated in the symptoms of RA (Darlington & Gamlin, 1996). However, the evidence that removing arachidonic and linoleic acids from the diet reduces RA symptoms is lacking (Darlington & Gamlin, 1996). Also, RA incidence decreased in Rochester, MN, USA, from 1950 to 1975

Abbreviation: RA, rheumatoid arthritis.

Corresponding author: Dr W. B. Grant, fax +1 757 864 7790, email wbgrant@norfolk.infi.net

(Linos *et al.* 1980), even though linoleic acid consumption in the USA rose significantly during that period (Food and Agriculture Organization, 1991).

n-3 Fatty acids such as eicosapentaenoic acid found in fish oil and α-linolenic acid found in some seeds (e.g. flaxseed and rapeseed oil), reduce inflammation and RA symptoms (DeLuca *et al.* 1995; Kremer, 1996; 2000; James & Cleland, 1997; James *et al.* 2000). Dihomo-γ-linolenic acid (20:3*n*-6), found in evening primrose (*Denothera biennis*), has a similar effect (Belch & Hill, 2000). The effect of *n*-3 fatty acids on inflammatory diseases may be due to the decrease in such inflammation mediators as eicosanoids and cytokines (DeLuca *et al.* 1995; Enders & Von Schacky, 1996). Shapiro *et al.* (1996) reported the results of case–control study that found baked or broiled fish to be associated with decreased risk of RA. The adjusted odds ratios for one to two or two or more servings of fish weekly compared with less than one serving weekly were 0·78 (95 % CI 0·53, 1·14) and 0·57 (95 % CI 0·35, 0·93) respectively. Assuming that one serving of fish is 120 g, this amount would equate to 20 g (752 kJ) fish oil per serving. Thus, reasonably large amounts of fish oil seem to be required to have an effect. These results were presented in support of the hypothesis that *n*-3 fatty acids could help prevent RA. James & Cleland (1997) make the case that dietary changes that increase the intake of *n*-3 fatty acids and reduce the intake of *n*-6 fatty acids can lead to both improvements in disease status and a reduction in the need for pharmaceutical drugs. Cleland & James (1997) also suggest that *n*-9 fatty acids (monounsaturated fatty acids, such as oleic acid found in olive oil), can be used to displace Ω-6 fatty acids from the diet.

Oxidative stress from free radicals attacking the synovial tissues is also involved in the expression of RA. Fe can be involved, leading to the increased generation of the hydroxyl radical (Mapp *et al.* 1995). Note that subjects who develop Alzheimer's disease often have elevated levels of transition metal ions in their brains, attributed to diets rich in acid-forming foods and high in energy intake (Grant, 1997, 1999*a*), and that Alzheimer's disease is linked to oxidative stress, including inflammation (Grant, 1997; Smith *et al.* 1997). In early rheumatoid synovitis, the amount of synovial membrane ferritin has been significantly associated with the activity of the disease at the time of biopsy (Blake *et al.* 1984). The authors conclude by stating that the use of multiple antioxidants would be helpful to relieve the discomfort of RA, among other approaches. This theory finds supports in part by Fernandes & Jolly (1998), who point out that energy restriction can reduce the production of reactive oxygen species.

The effectiveness of non-steroidal anti-inflammatory drugs seems to be related to their ability to prevent arachidonic acid from being metabolized to biologically-active eicosanoids (prostaglandins, thromboxanes and leukotrienes) by blocking cyclo-oxygenase activity (Cleland, 1991; McMillan *et al.* 1995).

To the extent that oxidative stress is involved in RA, increased intake of dietary or supplementary antioxidants should improve the status of those subjects with RA. Indeed, Heliövaara *et al.* (1994) found a low dietary antioxidant level to be a risk factor for RA. Hansen *et al.* (1998) found that those subjects with RA who increased their intake of fish and antioxidants reported improvement in the duration of morning stiffness, the number of swollen joints, the pain status and a reduced cost of medicine, while the doctors' global assessment, laboratory data, X-ray and the daily activities were unaltered.

Meat has been suggested as a possible contributing factor for RA in a number of studies. Sköldstam (1986) reported that of twenty Swedish RA patients put on a vegan diet for 3–4 months (seven used one to two cups of sour milk for breakfast), twelve reported improvement, five no change and three deterioration. Buchanan & Laurent (1990) point out that high-protein high-saturated-fat diets are implicated in the aetiology of RA. Kjeldsen-Kragh *et al.* (1991) found statistically significant improvement of RA symptoms among thirty-four patients who completed a 1-year vegetarian diet ($P < 0{\cdot}02$–$0{\cdot}0001$ for twelve tests). They also found improvement in disease status among diet responders in the second year of the study (Kjeldsen-Kragh *et al.* 1994). Garrett *et al.* (1993) reported that red meats are linked to worsened symptoms of RA. Kavanagh *et al.* (1995) reported that five of eleven RA patients who reported dietary exacerbation of RA symptoms, of twenty-four originally participating in the study (eleven dropped out between the 8th and 24th week), named red meat as the offending factor; no other factor was associated with more than four affected patients. Nenonen *et al.* (1998) reported that uncooked lactobacilli-rich vegan food decreased subjective symptoms of RA. A recent study by Kjeldsen-Kragh (1999) also showed that for all clinical variables and most laboratory variables measured, the twenty-seven patients in the fasting and vegetarian groups improved significantly ($P<0{\cdot}02$–$0{\cdot}0001$) compared with the twenty-six patients in the control group.

Ecological studies

In order to further investigate the link between meat consumption and RA, an ecological approach was used. In this approach a measure of disease at the national level is compared statistically with various components of national consumer food supply for a number of countries. This approach has been used to establish dietary links for several diseases: breast cancer with dietary fat early in life (Sasaki *et al.* 1993); colon cancer with animal fat as a risk factor (Armstrong & Doll, 1975); vegetable products as risk-reduction factors (Grant, 1999*b*); Alzheimer's disease with total energy and fat as the risk factors and fish and cereals as the risk-reduction factors (Grant, 1997). The ecological approach has also been used to confirm the results of other epidemiological studies. For example, Grant (1999*b*) used the ecological approach to examine the role of the non-fat portion of milk (risk factor) and tomatoes (risk-reduction factor) in the aetiology of prostate cancer as found by cohort studies (Giovannucci *et al.* 1998; Giovannucci, 1999). Grant (1999*d*) also found that milk protein had a positive correlation with hip fracture rates in thirteen countries, in general agreement with Feskanich *et al.* (1997) who reported that consumption of milk by women did not protect against hip fractures. The ecological approach must be applied carefully since both dietary risk

Table 1. Criteria for inclusion of rheumatoid arthritis (RA) prevalence studies in the multi-country analysis

1. The data appeared in Silman & Hochberg (1993)
2. The age range of >15 years should have been sampled
3. The population has the diet of a country recognized in the *Food Balance Sheets* (Food and Agriculture Organization, 1991)
4. The studies were conducted before 1987, the time at which the criteria for definite RA prevalence changed (Arnett *et al.* 1988)

and risk-reduction factors influence the outcomes, and since other non-dietary factors may be involved. It is important to include a large number of dietary factors and to carefully qualify the epidemiological data used in the analysis in order to obtain the best results.

The RA prevalence data-set used is taken from Silman & Hochberg (1993). This reference has a compilation of approximately fifty RA prevalence study results from African, Asian, European, North American and other populations. The criteria for inclusion in this multi-country analysis are given in Table 1. The countries that satisfy these criteria are shown in Table 2, along with the RA prevalence, the estimated year of the data collection and the reference.

For the dietary data, components of national dietary supply were derived from the FAO *Food Balance Sheets* (Food and Agriculture Organization, 1991). Data are collected from approximately 150 countries every 3 years. In the USA it has been determined recently that the human population consumes approximately 75 % of the available consumer food supply (the remaining 25 % spoils, is wasted, fed to pets and other animals etc.). It is assumed that similar factors apply to other countries. The survey data were from various years between 1975 and 1988, while the FAO data (Food and Agriculture Organization, 1991) were the average values for 1979–81. The different time periods could explain some of the differences. For example, total consumer fat supply in Italy increased from 118·6 g/person per d in 1975 to 144·4 g/person per d in 1988 (Food and Agriculture Organization, 1991).

Table 3. Statistical values (*P*)* using rheumatoid arthritis (RA) prevalence data for women from Silman & Hochberg (1993) and national dietary supply data from the Food and Agriculture Organization (1991) for the period 2 (−2) or 4 years before the RA prevalence data

	Fifteen countries			Eight countries		
	r^2	*F*	*P*	r^2	*F*	*P*
Meat fat energy (−2)	0·670	26·4	<0·001	0·877	42·8	<0·001
Meat fat energy	0·658	25·0	<0·001	0·874	41·6	<0·001
Meat fat (−2)	0·679	27·5	<0·001	0·845	32·8	<0·001
Meat fat	0·666	25·9	<0·001	0·837	30·8	<0·001
Meat energy	0·639	23·0	<0·001	0·828	28·4	<0·001
Meat	0·649	24·1	<0·001	0·795	23·3	0·002
Protein	0·562	16·6	0·001	0·685	13·0	0·011
Animal products	0·507	13·4	0·003	0·653	11·3	0·015
Animal fat energy	0·484	12·2	0·004	0·581	8·3	0·028

* Linear regression analysis (Student's *t* test).

The time delay between changes in consumption of particular foods and the development of chronic disease is an important consideration. For breast cancer it is the diet 10–20 years before incidence or mortality that appears to be most important (Sasaki *et al.* 1993). For Alzheimer's disease it is the diet near the time of development that seems to be most important (Grant, 1997; Smith *et al.* 1997). For RA the dietary supply values from 0, 2 and 4 years before the assumed dates for the RA prevalence studies were used in the analyses.

The statistical results are given in Table 3 and Fig. 1 for the period 2–4 years before the actual or assumed study data. Note that the 2-year delay results are slightly better than the 4-year delay results. In multiple linear regressions with any of the other components tested, meat and offal (termed meat) or meat fat always had the highest statistical

Table 2. Epidemiological data for both males and females for the eight and fifteen-country analyses of the relation between diet and rheumatoid arthritis (RA) prevalence

Country	Year*	Age range (years)	RA prevalence† (per 1000) Males	Females	Reference
Bulgaria	1966	>15	3·0	12·0	Tzonchev *et al.* (1968)
China	1980	>15	2·0	4·0	Beasley *et al.* (1983)
Czechoslovakia‡	1965	>15	3·0	5·0	Sitaj & Sebo (1968)
Denmark‡	1971	>15	4·0	12·0	Sorensen (1973)
Finland‡	1986	>15		20·0	Aho *et al.* (1989)
Germany‡§	1965	>15	16·0	5·0	Behrend *et al.* (1972)
Indonesia	1986	all		2·0 (2·5)	Darmawan (1988)
Japan	1965	>15	4·0	7·0	Kato *et al.* (1971)
Lesotho	1984	>15	0·0	4·0	Moolenburgh *et al.* (1986)
The Netherlands	1966	>15	5·0	12·0	den Oudsten (1968)
New Zealand‡	1968	>20	5·0 (4·5)	22·0 (20·0)	Prior *et al.* (1970)
Norway‡	1977	>15		7·0	Haavik (1979)
Sweden	1966	>15		9·0	Hellgren (1970)
UK‡	1959	>15	5·0	16·0	Lawrence (1961)
USA‡	1961	18–79	4·6 (4·3)	17·0 (16·0)	Engel (1968)

* The year was taken as 2–3 years before the publication date, unless better information was available.
† The RA prevalence was adjusted in some cases for the age distribution sampled, with the value used in the analyses given in parentheses.
‡ Countries used in the eight-country analysis.
§ Federal Republic of Germany.

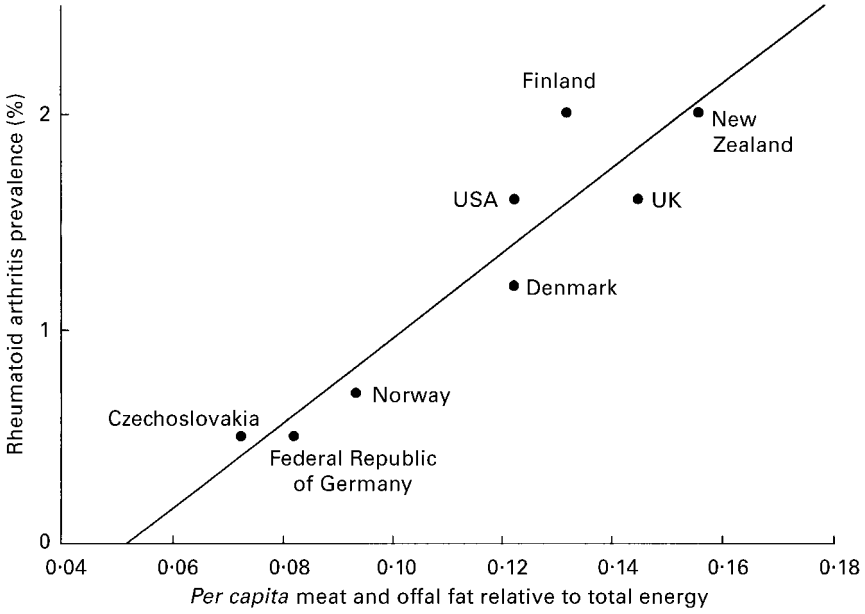

Fig. 1. Statistical results for rheumatoid arthritis prevalence *v.* meat and offal fat relative to total energy for female subjects from eight countries. r^2 0·877, $P < 0·01$.

significance. Meat fat comprised 58–81 % (mean 73 %) of meat energy for the countries used in the analysis. Other dietary components, such as fish, milk, sweeteners and vegetable oils, did not yield statistical results as good as that for animal fat relative to total energy.

The question always arises in such multi-country analyses as to whether countries with very different lifestyles, diets, medical systems etc., should be considered together in the analysis. Thus, for example, in the Alzheimer's disease study (Grant, 1997, 1999*a*), the inclusion of African and Asian countries in the analysis was questioned. When these countries were removed, leaving just seven European and North American countries, a stronger result was found, i.e. a multiple linear regression of total fat (high risk) and fish (risk reduction). Also, in IHD (Grant, 1998) and prostate cancer (Grant, 1999*c*) studies additional support for the dietary links was found by performing the statistical analyses on geopolitical groups of countries. For the RA study the approach taken was to reanalyse the data after the deletion of several countries with low dietary meat supply values, then look for the set of countries with the highest statistical correlation with RA

Table 4. Statistically significant associations between dietary meat or meat fat and sickness incapacity for work*† (Data from Table 1 of Leistner *et al.* 1986)

Country	Factors	r^2	F	P	Zero prevalence (energy; kJ/person per d)
Male					
Czechoslovakia	NS ($P > 0·05$)				
Czech Republic	NS ($P > 0·05$)				
Finland	Meat	0·794	34·6	<0·001	882
GDR	Meat (−2 years)	0·935	57·8	0·002	556
Slovakia	NS ($P > 0·05$)				
UK	No trend in sickness or meat				
Female					
Czechoslovakia	Meat fat	0·597	11·8	0·009	128
Czech Republic	Meat fat	0·400	5·3	0·05	–
Finland	Meat	0·914	96·2	<0·001	1007
	Meat fat	0·901	82·1	<0·001	765
GDR	Meat (−2 years)	0·976	106·7	<0·001	656
Slovakia	Meat fat (−2 years)	0·855	53·3	<0·001	489
UK	No trend in sickness or meat				
Male and female					
Poland	Meat (−4 years)	0·964	240·0	<0·001	610
Poland	Meat fat (−4 years)	0·959	211	<0·001	426

GDR, German Democratic Republic.
* Meat or meat fat energy consumption level at which there was zero prevalence.
† Student's *t* test.

prevalence. The countries removed as a result were primarily non-European countries (New Zealand and the USA remained), and two European countries with low meat consumption at the time of the study were also removed. Thus, all countries with a meat consumption of less than 1388 kJ (140 g)/person per d were removed. The statistical results for this set of eight countries are given in Table 3 and Fig. 1. Note that while the relative importance of the various dietary components was little changed, the correlation with RA prevalence increased dramatically. These data also indicate that the zero RA prevalence corresponds to a meat consumption of 803·3 kJ/person per d instead of 531 kJ/person per d when all fifteen countries are included in the analysis.

Temporal variations of diet and rheumatoid arthritis indices

There is another way to investigate whether meat or meat fat are associated with RA prevalence. Leistner *et al.* (1986) reported on such factors as sickness incapacity from work and hospital discharges for RA for the population of eight European countries for the period 1968–78. This period was long enough after the second World War that the infrastructure in Europe had been rebuilt and the buildings replaced such that prosperity was returning to the entire region and the population could spend more on food. The primary way this increased spending power was manifested in the diet was to add meat and reduce cereals and grains.

The statistical analysis of time series data for each country was done using data from Tables 1 (sickness incapacity for work) and 2 (hospital discharges) of Leistner *et al.* (1986). Data for each year were compared for dietary supply data and also for each year, but with a lag between diet and RA of 0, 2 or 4 years. Since cereals, fish, meat and meat fat were the main components changing, the analysis was centred on these variables. The results are shown in Table 4 for sickness incapacity for work. It was found that meat or meat fat, with an interval of from 0 to 4 years before the data, were statistically significantly associated with RA symptoms. In addition, the zero disease index intercept was in the range from 215 to 1007 kJ/person per d. While the rigor of the temporal analysis is less than that of the geographical analysis, and could not stand alone, it does support the geographical analysis.

Note that the results for Finland are based on values that include only subjects with a sickness incapacity of 7 d duration or longer. The data have a much lower incapacity rate (eleven to thirty persons per 1000 insured persons) than those for the Eastern European countries (61–143 persons per 1000 insured persons). The results show a slow down in the rate of RA increase above a meat energy level of 1672 kJ.

Discussion

Comments on the possible role of meat in the aetiology of rheumatoid arthritis

Since meat and meat fat have been found to have the highest dietary links to RA symptoms, it is worthwhile to try to identify the possible agent. Meat fat is a component likely to be responsible. However, meat fat has approximately the same lipid profile as dairy fat (Erasmus, 1993). While milk has been implicated as an exacerbating agent in inflammatory arthritis (Panush *et al.* 1986), milk, milk fat and animal fat were not found to be important factors in the analysis leading to the data in Table 3. This result suggests that meat fat may not be the primary agent giving rise to RA symptoms. Another possible agent in meat is nitrite. As pointed out by Lauer (1991), nitrite appeared in meat in Germany in the mid-nineteenth century. Saltpetre had been added to meat from about 1700, but sugar, which converts nitrate to nitrite, was added as early as 1825. RA was not common in antiquity (Roberts & Manchester, 1997). There was a rapid rise in the prevalence of RA in the mid-nineteenth century (Lauer, 1991). Increased concentrations of nitrate, nitrite and NO have been found in the serum and synovial fluid or urine of subjects with RA (Wigand *et al.* 1997). There appears to be no evidence that dietary nitrite leads to increased nitrite in the urine (Lee *et al.* 1986). However, there is evidence that subjects with RA have increased NO synthesis (Farrell *et al.* 1992). The two results may not be in conflict. A study in Finland found that cured meats were the primary source of 5·3 mg nitrite/d in the diet (Dich *et al.* 1996). The authors also reported that farmers consumed less nitrite than did white-collar workers and workers in industry. If increased dietary nitrite does lead to increased NO synthesis, it would support the role of nitrite in meat in the expression of RA symptoms. This finding could explain why urban dwellers in African populations generally have about twice the RA prevalence of those living in rural areas (Silman & Hochberg, 1993).

Since most of the population eat the same diet as those who suffer from RA, yet do not themselves have RA, and since dietary manipulation seems to reduce the symptoms of RA without curing it, there must be something in addition to the diet that gives rise to RA. It could be infection. For example, increases in serum antibodies have been found in subjects with RA (Chou *et al.* 1998). However, diet could still be related to the aetiology of RA. For example, animal products lead to different intestinal fauna and flora than do vegetable products (for a discussion, see Kjeldsen-Kragh, 1999). In addition, meat could also be involved in another way if nitrite is involved in the aetiology and not just in the severity of symptoms. It could also be that other components of meat could also be involved in the aetiology of RA.

Conclusion

The primary finding of the literature review and statistical analyses is that meat and offal may be a major risk factor for the expression of RA. The fats may contribute through inflammation or free radical production. However, since the lipid profiles of meat and dairy fatty acids are similar, and dairy fat is not found to be associated with RA symptoms, the fatty acids may not play as much of a role as has been generally thought. Nitrite is another possible agent that could lead to increased inflammation. The Fe in meat may also contribute by acting as a catalyst to increase the

production of free radicals. Finally, other components in meat may also be involved. Since the ecological approach is considered to be useful for developing hypothesis, it is hoped that the results presented here will lead to further case–control and clinical studies to investigate the aeitiology of RA and the possible role of meat.

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References

Ahoiid K, Heliovaara M, Sievers K, Maatela J & Isomaki H (1989) Clinical arthritis associated with positive radiological and serological findings in Finnish adults. *Rheumatism International* **9**, 7–11.

Armstrong B & Doll R (1975) Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *International Journal of Cancer* **15**, 617–631.

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF & Cooper NS (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheumatism* **31**, 315–324.

Beasley RP, Bennett PH & Chun Lin C (1983) Low prevalence of rheumatoid arthritis in Chinese. Prevalence survey in a rural community. *Journal of Rheumatology* **10**, Suppl., 11–15.

Behrend T, Lawrence JS, Behrend H & Fischer K (1972) Prevalence of rheumatoid arthritis in rural Germany. *International Journal of Epidemiology* **1**, 153–156.

Belch JJF & Hill A (2000) Evening primrose oil and borage oil in rheumatologic conditions. *American Journal of Clinical Nutrition* **71**, Suppl., 352S–356S.

Blake DR, Gallagher PJ, Potter AR, Bell MJ & Bacon PA (1984) The effect of synovial iron on the progression of rheumatoid disease. A histologic assessment of patients with early rheumatoid synovitis. *Arthritis and Rheumatism* **27**, 495–501.

Buchanan A & Laurent RM (1990) Rheumatoid arthritis: an example of ecological succession. *Canadian Bulletin of Medical History* **7**, 77–91.

Chou CT, Uksila J & Toivanen P (1998) Enterobacterial antibodies in Chinese patients with rheumatoid arthritis and ankylosing spondylitis. *Clinical Experimental Rheumatology* **16**, 161–164.

Cleland LG (1991) Diet and arthritis. *Current Therapeutics* **32**, 51–56.

Cleland LG & James MJ (1997) Rheumatoid arthritis and the balance of dietary *n*-6 and *n*-3 essential fatty acids. *British Journal of Rheumatology* **36**, 513–515.

Darlington LG & Gamlin L (1996) In *Diet and Arthritis.* London: Vermilion.

Darlington LG, Ramsey NW & Mansfield JR (1986) Placebo-controlled, blind study of dietary manipulation therapy in rheumatoid arthritis. *Lancet* **i**, 236–238.

Darmawan J (1988) Rheumatic conditions in the northern part of central Java. An epidemiological survey. Ph.D Thesis, Erasmus University, Rotterdam, The Netherlands.

DeLuca P, Rothman D & Zurier RB (1995) Marine and botanical lipids as immunomodulatory and therapeutic agents in the treatment of rheumatoid arthritis. *Rheumatic Disease Clinics of North America* **21**, 759–777.

den Oudsten SA, Planten O & Posthuyma EPS (1968) Longitudinal survey of RA in an urban district of Rotterdam. In *Population Studies of the Rheumatic Diseases*, vol. 15, pp. 99–105 [PH Bennett and PHN Wood, editors]. Amsterdam: Excerpta Medica.

Dich J, Jarvinen R, Knekt P & Penttila PL (1996) Dietary intakes of nitrate, nitrite and NDMA the Finnish Mobile Clinic Health Examination Survey. *Food Additives and Contaminants* **13**, 541–552.

Enders S & Von Schacky C (1996) *n*-3 Polyunsaturated fatty acids and human cytokine synthesis. *Current Opinion in Lipidology* **7**, 48–52.

Engel A1968 Rheumatoid arthritis in US adults. In *Population Studies of the Rheumatic Diseases*, p. 83 [PH Bennett and PHN Wood, editors]. Amsterdam: Excerpta Medica.

Erasmus U (1993) In *Fats That Heal, Fats That Kill*. Burnaby, BC: Alive Books.

Farrell AJ, Blake DR, Palmer RMJ & Moncada S (1992) Increased concentrations of nitrite in synovial fluid and serum samples suggest increased nitric oxide synthesis in rheumatic diseases. *Annals of the Rheumatic Diseases* **51**, 1219–1222.

Fernandes G & Jolly CA (1998) Nutrition and autoimmune disease. *Nutrition Reviews* **56**, S161–S169.

Feskanich D, Willett WC, Stampfer JJ & Colditz GA (1997) Milk, dietary calcium, and bone fractures in women: a 12-year prospective study. *American Journal of Public Health* **87**, 992–997.

Food and Agriculture Organization (1991) *Food Balance Sheets*. Rome: FAO.

Fox DA (1997) Rheumatoid arthritis – heresies and speculations. *Perspectives in Biology and Medicine* **40**, 479–491.

Garrett SL, Kennedy LG & Calin A (1993) Patient's perceptions of disease modulation by diet in inflammatory (rheumatoid arthritis/ankylosing spondylitis) and degenerative arthropathies. *British Journal of Rheumatology* **32**, Suppl. 2, 43.

Giovannucci E (1999) Tomatoes, tomato-based products, lycopene, and cancer: Review of the epidemiologic literature. *Journal of the National Cancer Institute* **91**, 317–331.

Giovannucci E, Rimm EB, Wolk A, Ascherio A, Stampfer MJ, Colditz GA & Willett WC (1998) Calcium and fructose intake in relation to risk of prostate cancer. *Cancer Research* **58**, 442–447.

Grant WB (1997) Dietary links to Alzheimer's disease. *Alzheimer's Disease Review* **2**, 42–55. http://www.coa.uky.edu/ADReview/contents.htm.

Grant WB (1998) The role of milk and sugar in heart disease. *American Journal of Natural Medicine* **5**, 19–23.

Grant WB (1999*a*) Dietary links to Alzheimer's disease: 1999 update. *Journal of Alzheimer's Disease* **1**, 197–201.

Grant WB (1999*b*) Dietary fiber and colorectal cancer. *The Townsend Letter for Doctors and Patients* **192**, 112–113.

Grant WB (1999*c*) An ecologic study of dietary links to prostate cancer. *Alternative Medicine Review* **4**, 162–169.

Grant WB (1999*d*) Lactose maldigestion and calcium from dairy products. *American Journal of Clinical Nutrition* **70**, 301–302.

Haavik T (1979) Rheumatoid arthritis in a Norwegian county. A study based on the local doctor's files. *Scandinavian Journal of Rheumatology* **8**, 184–186.

Hansen G, Nielson L, Kluger E, Thysen MH, Emmertsen H, Stengard-Pedersen K, Lund EC, Unger B & Andersen PW (1998) Nutritional status of Danish patients with rheumatoid

arthritis and effects of a diet adjusted in energy intake, fish content and antioxidants (in Danish). *Ugeskr Laeger* **160**, 3074–3078.

Heliövaara M, Knekt P, Aho K, Aaran R-K, Alfthan G & Aromaa A (1994) Serum antioxidants and risk of rheumatoid arthritis. *Annals of Rheumatic Diseases* **53**, 51–53.

Hellgren L (1970) Prevalence of rheumatoid arthritis in different geographical areas of Sweden. *Acta Rheumatologica Scandinavica* **16**, 293–303.

Henderson CJ & Panush RS (1999) Diets, dietary supplements, and nutritional therapies in rheumatic diseases. *Rheumatic Disease Clinics of North America* **25**, 937–968.

James MJ & Cleland LG (1997) Dietary *n*-3 fatty acids and therapy for rheumatoid arthritis. *Seminars in Arthritis and Rheumatism* **27**, 85–97.

James MJ, Gibson RA & Cleland LG (2000) Dietary polyunsaturated fatty acids and inflammatory mediator production. *American Journal of Clinical Nutrition* **71**, Suppl., 343S–348S.

Kato H, Duff IF, Russell WJ, Uda Y, Hamilton HB, Kawamoto S & Johnson KG (1971) Rheumatoid arthritis and gout in Hiroshima and Nagasaki Japan. A prevalence and incidence study. *Journal of Chronic Disease* **23**, 659–679.

Kavanagh R, Workman E, Nash P, Smith M, Hazleman BL & Hunter JO (1995) The effects of elemental diet and subsequent food reintroduction on rheumatoid arthritis. *British Journal of Rheumatism* **34**, 270–273.

Kjeldsen-Kragh J (1999) Rheumatoid arthritis treated with vegetarian diets. *American Journal of Clinical Nutrition* **70**, 594S–600S.

Kjeldsen-Kragh J, Haugen M, Borchgrevink CF & Førre Ø (1994) Vegetarian diet for patients with rheumatoid arthritis – status: two years after introduction of the diet. *Clinical Rheumatology* **13**, 475–482.

Kjeldsen-Kragh J, Haugen M, Borchgrevink CF, Laerum E, Eek M, Mowinkel P, Hovi K & Førre Ø (1991) Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. *Lancet* **338**, 899–902.

Kremer JM (1996) Effects of modulation of inflammatory and immune parameters in patient with rheumatic and inflammatory disease receiving dietary supplementation of *n*-3 and *n*-6 fatty acids. *Lipids* **31**, S243–S247.

Kremer JM (2000) N-3 Fatty acid supplements in rheumatoid arthritis. *American Journal of Clinical Nutrition* **71**, Suppl., 349S–351S.

Lawrence JS (1961) Prevalence of rheumatoid arthritis. *Annals of the Rheumatic Diseases* **20**, 11–17.

Lauer K (1991) The history of nitrite in human nutrition: a contribution from German cookery books. *Journal of Clinical Epidemiology* **44**, 261–264.

Lee K, Greger JL, Consaul JR, Graham KL & Chinn MS (1986) Nitrate, nitrite balance, and de novo synthesis of nitrate in human consuming cured meats. *American Journal of Clinical Nutrition* **44**, 188–194.

Leistner K, Wessel G & Allander E (1986) Medium-term trends in the occurrence of rheumatic diseases in European countries. *Scandinavian Journal of Rheumatology* **15**, 206–218.

Linos A, Worthington JW, O'Fallon WM & Kurland LT (1980) The epidemiology of rheumatoid arthritis in Rochester Minnesota: a study of incidence, prevalence, and mortality. *American Journal of Epidemiology* **111**, 87–98.

McMillan RM, Foster SJ & Shaw JS (1995) Approaches to novel anti-arthritic drugs by modulation of the arachidonic acid cascade. In *Mechanisms and Models in Rheumatoid Arthritis*, pp. 283–300 [B Henderson, JCW Edwards and ER Pettipher, editors]. London: Academic Press.

Mapp PI, Grootveld MC & Blake DR (1995) Hypoxia, oxidative stress and rheumatoid arthritis. *British Medical Bulletin* **51**, 419–436.

Moolenburgh JD, Valkenburg HA & Fourie PB (1986) A population study on rheumatoid arthritis in Lesotho, southern Africa. *Annals of the Rheumatic Diseases* **45**, 691–695.

Nenonen FT, Helve TA, Tauma A-L & Hänninen OO (1998) Uncooked, lactobacilli-rich, vegan food and rheumatoid arthritis. *British Journal of Rheumatology* **37**, 274–281.

Panush RS (1997) Diet therapy and other questionable remedies for arthritis. In *Arthritis and Allied Conditions. A Textbook of Rheumatology* 13th ed., pp. 857–870 [WJ Koopman, editors]. Baltimore, MD: Williams and Wilkins.

Panush RS, Stroud RM & Webster EM (1986) Food-induced (allergic) arthritis. Inflammatory arthritis exacerbated by milk. *Arthritis and Rheumatism* **29**, 220–226.

Prior IAM, Evans JG, Morrison RBI & Rose BS (1970) The carteron study: six patterns of vascular, respiratory, rheumatic and related abnormalities in a sample of New Zealand European adults. *New Zealand Medical Journal* **72**, 169–177.

Roberts C & Manchester K (1997) In *The Archaeology of Disease,* 2nd ed., pp. 116–118, Ithaca, NY: Cornell University Press.

Sasaki S, Horacsek M & Kestellot H (1993) An ecological study of the relationship between dietary fat intake and breast cancer mortality. *Preventive Medicine* **22**, 187–202.

Shapiro JA, Koepsell TD, Voigt LF, Dugowson CE, Kestin M & Nelson JL (1996) Diet and rheumatoid arthritis in women: a possible protective effect of fish consumption. *Epidemiology* **7**, 256–263.

Silman AJ & Hochberg MC (1993) In *Epidemiology of the Rheumatic Diseases*, pp. 7–68. Oxford: Oxford University Press.

Sitaj S & Sebo M (1968) Rheumatoid arthritis and ankylosing spondylitis in Czechoslovakia. In *Population Studies of the Rheumatic Diseases*, pp. 64–68 [PH Bennettand PHN Wood, editors]. Amsterdam: Excerpta Medica.

Sköldstam L (1986) Fasting and vegan diet in rheumatoid arthritis. *Scandinavian Journal of Rheumatology* **15**, 219–223.

Smith MA, Petot GJ & Perry G (1997) Diet and oxidative stress: a novel synthesis of epidemiological data on Alzheimer's disease. *Alzheimer's Disease Review* **2**, 58–59.

Sorensen K (1973) Rheumatoid arthritis in Denmark: two population studies. *Danish Medical Bulletin* **20**, 86–93.

Tzonchev VT, Pilossoff T & Kanev K (1968) Prevalence of inflammatory arthritis in Bulgaria. In *Population Studies of the Rheumatic Diseases*, p. 363 [PH Bennett and PHN Wood, editors]. Amsterdam: Excerpta Medica.

Wigand R, Meyer J, Busse R & Hecker M (1997) Increased serum N^G-hydrocy-L-arginine in patients with rheumatoid arthritis and systemic lupus erythematosus as an index of an increased nitric oxide synthase activity. *Annals of the Rheumatic Diseases* **56**, 330–332.