that rest was the important factor, but in the first two or three months of their treatment it was obvious that stimulation was more important in relieving pain than rest was.

It seems that patients with the most severe pain do not get relief from electrical stimulation. We have seen six patients (not included in this series) who found straight away that the electric stimulation merely added to their pain. Other patients felt the tingling paraesthesiae and their pain but there was no interaction between the two. Those who got relief from stimulation did not feel the pain while they felt the paraesthesiae or else they felt less pain. It may be that in those patients in whom electrical stimulation increased the pain there were insufficient large myelinated fibres surviving to produce the inhibition and when any fibres were stimulated it was the small myelinated fibres.

Results with continuous electric stimulation were compared with those with cold spray, vibration, repeated injections of the tender area with local anaesthetic solution, and rubbing the skin or tender area. No relation between all these ways of alleviating the pain was found.

An examination of the cases in which stimulation was stopped showed that there were two groups of patients who do not want this treatment: those with the most severe pain in whom stimulation either had no effect or it made the pain worse and those with the least severe pain for whom the whole inconvenience of constant stimulation did not justify their efforts.

Discussion

Our success with temporary treatment of certain patients with severe post-herpetic neuralgia does not mean that electric stimulation is better than sprays or vibration. The patients chosen for testing electric stimulation were those in which these other forms of stimulation had continually failed. There are cases in which either or both work, and some patients who had electric stimulation considered that vibration or cold sprays were better.

The method has certain disadvantages. The apparatus is expensive, and it is a nuisance to have to carry it around and to wear electrodes attached to the skin. Some old people have refused to take the apparatus as they are frightened of electricity. Patients tend to be disappointed for they expect a cure and are given alleviation.

The mechanism that underlies prolonged relief of pain for hours after stopping stimulation is not understood. From studies of neuromas induced in the rat Wall and Gutnick (1974) have proposed that electric stimulation may silence abnormal generators of nerve impulses in the peripheral nerve itself. They found that a tetanus delivered to the nerve for seconds stopped spontaneous firing for six minutes. The mechanism of the improvement in the whole course of the post-herpetic neuralgia is even more of a puzzle. Possibly prolonged stimulation induces changes in the peripheral nerve itself or it may be that central structures, relieved of a continuous afferent barrage, may sink back to normal excitabilitv.

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Vitamin D and Myocardial Infarction

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Summary

A detailed investigation was carried out into the consumption of vitamin D from different sources in patients who had suffered from myocardial infarction, angina pectoris, and degenerative joint diseases. Randomly selected controls of the same ages and sex were drawn from the Central Bureau of Statistics. The consumption was significantly higher in infarction patients. A daily intake of 30 μg may be the critical level. Student's t test for trend showed increasing probability of myocardial infarction with increasing intake of vitamin D, and more infarction patients than controls had a history of kidney stone. Long-term high consumption of vitamin D may be a precipitating cause of myocardial infarction.

Introduction

It is well known that vitamin D produces serious toxic effects if consumed for a period in grossly excessive amounts (Lowe *et al.*, 1954; Fellers and Schwartz, 1958; Smith *et al.*, 1959; Lowe, 1965; Kaserer *et al.*, 1966; Seelig, 1969). On the basis of such data The Committee on Nutrition of the American Academy of Pediatrics (1963) recommended the discontinuation of the practice of enriching food other than milk and infant food. The long-term consequences of consumption of more than the recommended allowance of 10 μg a day in adults are entirely unknown.

Dalderup *et al.* (1965), Feenstra and Wilkens (1965), and Palmisano (1973) showed that the consumption of cod liver oil and vitamin D preparations raises serum cholesterol. Cholesterol is probably converted into 7-dehydrocholesterol (vitamin D_3) in vivo (Glover *et al.*, 1952). Dalderup *et al.* (1965) and Knox (1973) suggested an association between vitamin D consumption and death from ischemic heart disease. Patients with hypercalcaemia because of vitamin D intoxication are likely to develop renal calculi. Lindén (1972) and Westlund (1973) found an association between urolithiasis and coronary heart disease. Kinley and Krause (1959) found that vitamin A may lower serum cholesterol levels, and Ross and Campbell (1961) suggested that a relative vitamin A deficiency may cause coronary heart disease. Very little is, however, known of the interrelationship between vitamin A and D in vivo.

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Hess (1922) was the first to prove that sunlight could cure rickets. Hess and Weinstock (1925) found that skin exposed to ultraviolet rays has an antirachitic property. The presence of vitamin D in the skin suggested to Loomis (1967) that the rate of conversion of 7-dehydrocholesterol to vitamin D in the skin is regulated by pigmentation and keratinization of the stratum corneum, which allow only regulated amounts of ultraviolet radiation to reach the region where vitamin D is synthesized. Adaptation to the variable intensities of solar ultraviolet light in the North requires not only winter depigmentation but also summer repigmentation to keep the rate of vitamin D synthesis constant throughout the year.

Few studies have been concerned with the consumption of vitamin D in the general population. Dale and Lowenberg (1967) found that daily average intake in 150 randomly selected people below the age of 17 was about 12·5 μg regardless of age. Fomon (American Academy of Pediatrics, 1963) found that children in North America are likely to receive more than 30 μg/day. As coronary heart disease is a major problem the investigation of risk factors other than fats and genetics seems important.

This paper describes the findings in a detailed investigation of the vitamin D consumption of people who had suffered from myocardial infarction compared with the consumption of some other groups. The study was carried out in northern Norway, where myocardial infarction has a higher death rate than in the remainder of the country and where natural food provides an important source of vitamin D. In 1964-7 the age-adjusted death rate from A 81 (Arteriosclerotic and degenerative heart disease, I.C.D.) Seventh Revision for men aged 40-69 was 51% above the national mean in Finnmark and 23% above the national mean in the county of Troms—from which the present material was collected.

Subjects

The subjects were all people living in the Troms area who during the years 1967-72 had qualified for disability pension because of myocardial infarction, angina pectoris, or degenerative joint diseases. The three groups numbered 150 (118 men and 32 women), 88 (43 men and 45 women), and 103 (34 men and 69 women) respectively. The controls were randomly selected residents of the Tromso area of the same age and sex as the above people. Controls who had previously suffered myocardial infarction or angina pectoris were deliberately excluded.

Methods

A tabulated form was designed to record the intake of vitamin D from different sources—vitamin D preparations, natural food, and fortified food. The information concerned was obtained entirely from the people themselves. They were visited in their homes or contacted by telephone or by letter on two or more occasions. Some kept in contact with the author by seeing him in his office several times. Careful instructions were given and the recording procedure explained.

Each person was asked to record his consumption of vitamin D preparations according to a complete list which was given him. He was asked to record how many capsules or teaspoons he used daily of each preparation, for how many months a year, and for how many years. Since long-term consumption was of special interest intakes which had lasted a few months or which had begun after the onset of myocardial infarction or angina pectoris were not recorded, but there were only three people with such intakes.

The consumption of vitamin D preparations varied according to the season though about 50% of the people consumed the same preparations in the same doses all the year round. For those whose consumption varied with the season an estimation was made of average daily intake during the year. There is a high consumption of commercial vitamin D preparations in northern Norway because of the arctic climate in which sunlight can not be relied on to provide year-round protection.

The natural food source of vitamin D which made the greatest contribution was fish liver prepared in a special way. Fish liver is a common dish in most homes in northern Norway. Ten families were chosen at random and visited to study the preparation of this particular dish, which served as the main meal from one to three times a week. About 100-200g fish liver per capita is boiled for one to two hours. The Section for Research, Norwegian Department of Fisheries, estimates that 100 g fish liver boiled for one hour provides 50 g oil, each gram containing 1·25 μg vitamin D. To calculate the intake of vitamin D through this dish it was important to record the amount of fish liver consumed by each subject. Generally a dish of this meal will provide 62·5-125 μg.

In Norway only margarine and a few sandwich spreads are fortified—magarine with 62·5 μg/kg. The recordings took into account the purchase of such food.

Results

The data showed widespread average daily intakes for the various groups as well as variability in the daily intakes for the individual subjects. The average daily intake for the matched male controls was 22·68 μg and for the matched female controls 20·68 μg. The corresponding figures for infarction patients were 31·28 μg and 34·05 μg respectively. The range of the daily intakes for matched male infarction patients born 1915-19, who as a group had the highest average daily intake (43·53 μg), was 0 μg to 98·25 μg. Men suffering from angina pectoris had as a group the lowest intakes (16·78 μg, range 0 μg to 49·38 μg). The average amount of vitamin D contributed by each source for each group is shown in table I. Vitamin D preparations and natural food were for all groups the main sources of vitamin D.

The infarction patients had higher average daily intakes than

TABLE I—*Average Daily Intakes and Contributing Sources of Vitamin D for People with Myocardial Infarction, Angina Pectoris, and Degenerative Joint Diseases and Matched Controls*

Group	No.	Total Average Daily Intake (μg)	Vitamin D Preparations (μg)	Food Sources (μg)		
				Fortified	Natural	Total
			Men			
Infarction	118	31·28	14·80	3·28	13·20	16·48
Control	118	22·68	11·03	2·53	9·13	11·66
Angina pectoris	43	16·78	7·80	3·03	5·95	8·98
Control	43	23·23	13·78	2·55	6·90	9·45
Degenerative joint diseases	34	24·83	12·60	2·98	9·25	12·23
Control	34	26·63	15·48	2·55	8·60	11·15
			Women			
Infarction	32	34·05	23·80	2·83	7·43	10·26
Control	32	20·68	15·23	2·05	3·43	5·46
Angina pectoris	45	25·95	19·23	3·03	3·30	6·73
Control	45	24·13	17·95	2·35	3·83	6·18
Degenerative joint diseases	69	20·03	11·98	2·90	5·15	8·05
Control	69	22·38	16·70	2·70	2·95	5·65
Total excluding infarction patients	532	22·60	16·95	2·75	2·90	5·65

TABLE II—*Paired Comparisons between Daily Intakes of Vitamin D in Infarction Patients and Matched Controls according to Age*

Born	No.	Mean Difference (μg)	S.D.	S.E. of Mean	t	P
			Men			
Before 1905	37	6·68	28·82	4·74	1·41	0·2 >P>0·1
1905-9	35	0·21	24·60	4·16	0·05	P>0·8
1910-4	14	1·29	23·23	6·21	0·21	P>0·8
1915-59	21	27·40	28·30	6·18	4·44	P<0·001
After 1919	11	15·23	15·69	4·73	3·22	0·01 >P>0·005
Total	118	8·61	27·30	2·51	3·42	P<0·001
			Women			
Before 1905	11	8·58	31·86	9·61	0·89	
1905-14	15	17·91	22·18	5·73	3·13	0·005>P>0·0025
After 1914	6	9·58	17·27	7·05	1·36	
Total	32	13·14	24·87	4·40	2·99	0·005>P>0·0025

all other groups. To study the differences more closely the *t* test was applied to a paired comparison of differences in daily intakes between male and female infarction patients and the corresponding matched controls (table II). The differences in daily intakes between male and female infarction patients and their corresponding matched controls were highly significant (P <0·001 and P> 0·0025 respectively). No significant differences were found when a paired comparison was made for either sex between angina pectoris patients and matched controls or between patients suffering from degenerative joint diseases and matched controls.

A daily intake of 30 μg vitamin D may be incriminated as a critical level. When a comparison was made between male infarction patients and matched controls with regard to daily intakes of more or less than 30 μg the difference was found to be highly significant (χ^2 (with Yates's correction) = 7·02, P <0·001; table III). Comparable findings were made for the women (P <0·001).

TABLE III—*Paired Comparison of daily Intakes of Vitamin D in 118 Male Infarction Patients and 118 Matched Controls*

Infarction Patients	Controls		Total
	>30 μg	<30 μg	
>30 μg	13	39	52
<30 μg	18	48	66
Total	31	87	118

The natural prophylactic agent, sunlight, was not included in the computation of vitamin D intakes, but a comparison was made between people who said that they did and those who said they did not tan easily when exposed to the sun. More people in the infarction groups had a low susceptibility to pigmentation than among the matched controls. The difference was highly significant (men χ^2 = 8·36, P <0·004; women P <0·001; table IV). In the groups of angina pectoris patients and patients suffering from degenerative joint diseases and their corresponding matched controls no difference was found with regard to this variable. When the two variables—high or low susceptibility to cutaneous pigmentation and daily intakes of more or less than 30·0 μg—were studied together in male subjects the trend for increasing risk of myocardial infarction with increasing consumption of vitamin D was found to be highly significant in the group that tanned easily (χ^2 = 8·50, P = 0·0035) and for the total of the two pigmentation groups (χ^2 = 13·93, P = 0·0002). For the group that did not tan easily the probability figure was 0·03 (χ^2 = 4·77; table V). Comparable findings were made for the women. For the angina pectoris patients and their matched controls and for patients with degenerative joint diseases and their matched controls no such trends were found.

TABLE IV—*Susceptibility to Cutaneous Pigmentation in 118 Male Infarction Patients and 118 Matched Controls*

Susceptibility to Pigmentation	Infarction Patients	Controls	Total
High	56	78	134
Low	62	40	102
Total	118	118	236

Among the 150 infarction patients there were 25 with a history of kidney stone. Among the remaining 532 of the study population there were 51 with a history of kidney stone (χ^2 = 7·71, P = 0·006). The patients who had suffered from urolithiasis had a higher average daily intake (29·13 μg) than the rest (22·48 μg), and more had a daily intake above 30 μg.

Discussion

This study originated in the idea that long-term consumption of high doses of vitamin D might be a precipitating cause of myocardial infarction. So far the hypothesis is strongly supported. It was necessary to take into account the consumption of vitamin D from various sources as well as the production by the skin. It should be remembered that vitamin D resembles the hormones more closely than it resembles the dietary vitamins since it is practically absent in ordinary food and is produced by an organ, the skin, and then distributed by the blood stream for action elsewhere in the body.

The epidemic of myocardial infarction began in the late 1920s, and it was not until 1920 that Mellanby showed that cod liver oil would prevent rickets; and Hess (1922) was the first to prove that sunlight could cure rickets. The increasing consumption of vitamin D started in the 1920s, in Norway margarine has been fortified since 1922, and the consumption of various vitamin D preparations has been steadily increasing. During the war cod liver oil was rationed in this country.

TABLE V—*Daily Intake of Vitamin D in 118 Male Infarction Patients and 118 Matched Controls according to Susceptibility to Pigmentation*

Vitamin D Intake (μg)	Susceptibility to Cutaneous Pigmentation					
	High			Low		
	Infarction Patients	Controls	Total	Infarction Patients	Controls	Total
<10	8	24	32	11	9	20
10-20	11	22	33	13	13	26
-30	13	13	26	10	6	16
-40	8	8	16	7	8	15
-50	8	6	14	12	3	15
>50	8	5	13	9	1	10
Total	56	78	134	62	40	102

There seems to be contradiction between these suggestions and the findings of the importance of genetic factors. There is an inborn racial and individual difference in the sensitivity to vitamin D as well as in the ability of the skin to pigment and form keratin (Witkop 1967).

A striking difference appeared between infarction patients and those who suffered from angina pectoris despite the fact that angina pectoris, like myocardial infarction, is associated with high serum cholesterol levels. The overall physiological activity of vitamin D is, however, to raise serum calcium and phosphate. Blood cholesterol can be lowered by increasing calcium intake (Yacowitz, 1965).

As far as the cholesterol metabolism is concerned there may be metabolic antagonism between vitamin A which lowers serum cholesterol and vitamin D which raises it. Since fish liver contains high concentrations of vitamin A an intake deficiency of this vitamin is unlikely to be of major importance in the Tromso area.

Various national committees (British Medical Association, 1950; *Canadian Bulletin on Nutrition*, 1953; American Academy of Pediatrics, 1963, 1965) have recommended the discontinuation of fortifying food with vitamin D. In the present study fortified food provided only a minor part of the individual vitamin D consumption. An attempt should be made to restrict the intake from all sources save from the production of the skin. Efforts should particularly be made to dispel the concept of vitamin D preparations as tonics, and consideration should be given to the ease with which vitamin D preparations can be acquired through commercial sale.

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Blood Levels and Management of Lithium Treatment

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Summary

The limited value of plasma measurements in the management of treatment with lithium is discussed in the light of the mechanisms of its therapeutic actions and toxic effects.

The plasma level of lithium usually rises twofold or threefold in the three to five hours after ingestion of each dose of delayed-release tablets and then gradually falls. The precise shape and height of the lithium curve depend on gastric emptying, which can be slowed with propantheline or speeded with metoclopramide. Depressed or demented patients may be irregular in taking their tablets and variable in food intake. Both the time of the blood test and this behaviour must be considered before changing the prescribed dose of lithium salt because of a laboratory result. A lithium tolerance curve may be a safer guide to treatment than single measures.

Mild intermittent thirst is a common early side effect, and severe persistent thirst with polyuria is an uncommon later effect of daily intakes of at least 1,500 mg lithium carbonate. This diabetes insipidus is reversible, non-progressive, unrelated to plasma level, and distinct in attack from lithium-induced hypothyroidism, which may occur at low dosage but is also usually of late onset and reversible or treatable with thyroxine while lithium is continued. Obesity is another occasional effect of large doses. These side effects and the antimanic and prophylactic effects may have different mechanisms.

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Introduction

Lithium carbonate (or in some countries lithium sulphate or lithium citrate) is now very widely used for the control of manic symptoms (excitement) and for the prevention of further manic or depressive episodes in patients who have suffered frequently recurring attacks of either syndrome alone or both in turn. In prophylaxis the drug is often taken for many months or years in the course of ordinary life, and sustained or delayed-release tablets which need be taken only once a day (at breakfast or bedtime) are often preferred to the usual oral tablets which require regular eight-hourly, or sometimes 12-hourly ingestion.

Since lithium can insidiously produce a dangerously toxic state with symptoms of mental dulling and confusion, slurred speech, and ataxia it is customary to measure the patient's plasma lithium concentration at intervals to keep it below 2·0 mEq/l. at all times and preferably within a so-called therapeutic range of 0·6-1·5 mEq/l. or 0·8-1·2 mEq/l. (Coppen *et al.*, 1969; Baastrup *et al.*, 1970; Fry and Marks, 1971). We have observed errors of management, however, when patients have received dangerously too much or uselessly too little lithium because of failure to realize how quickly plasma levels of lithium can