Comment

The absence of antibody to HTLV-I and HIV in patients with multiple sclerosis from France and similar findings in Italian patients (L Chieco-Bianchi *et al*, personal communication) argue against these viruses having a role in the development of multiple sclerosis. Furthermore, the negative results in patients from the French West Indies, an area endemic for HTLV-I, strengthen the lack of a serological association between HTLV-I and multiple sclerosis.

Epidemiologically, the geographical distributions of multiple sclerosis and HTLV-I are quite different. Areas endemic for HTLV-I are mainly south western Japan, the Caribbean regions, and central Africa, countries where multiple sclerosis is virtually absent. In Japan the prevalence of infection with HTLV-I has a north-south gradient but that of multiple sclerosis does not.[5] Furthermore, HTLV-I is not endemic north of 40° latitude, either in Europe or in America, which are known as high risk areas for multiple sclerosis. If epidemiological data suggest that there is an association between multiple sclerosis and an infectious agent, probably viral, then a retrovirus other than HTLV-I and HIV might be responsible.

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ADDENDUM—Recent reports in *Nature* (10 July 1986: Hauser *et al*, p 176 and Karpas *et al*, p 177) confirm the lack of an association between HTLV-I and multiple sclerosis, based on molecular virological data.

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Muscle damage induced by isotretinoin

Since the introduction of isotretinoin (13-cis-retinoic acid), a synthetic analogue of vitamin A, for the treatment of nodulocystic acne and several disorders of keratinisation an increasing number of adverse reactions have been reported. About 15% of patients treated with isotretinoin have developed musculoskeletal symptoms and on rarer occasions increased creatine kinase activities.[1] A causal relation between the drug and increased creatine kinase activity has not been established, however, owing to lack of adequate data.

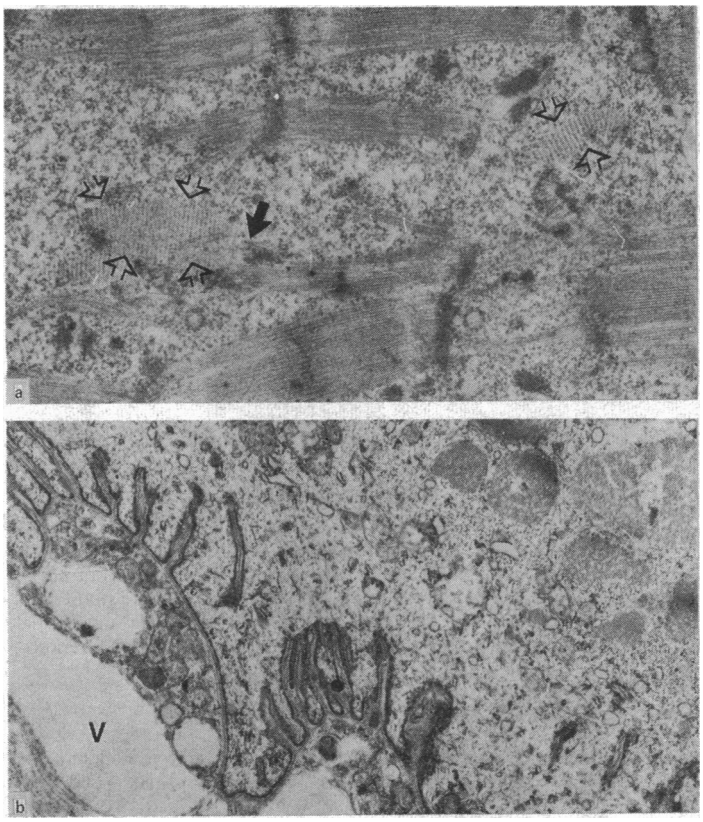
We describe two patients with nodulocystic acne who showed clinical and electromyographic evidence of muscle damage during treatment with isotretinoin. In one patient the muscle damage was confirmed by histological and ultrastructural findings. We believe that this is the first neuromuscular study to show muscle damage induced by isotretinoin.

Case reports

Two young men (aged 16 and 20) presented with recalcitrant nodulocystic acne unresponsive to various types of treatment, all of which had been discontinued several weeks previously. At presentation, apart from severe acne lesions over the face, chest, and back, physical examination and a complete neurological evaluation were unremarkable. Results of laboratory investigations were normal. Treatment with oral isotretinoin 40 mg daily (0·5 mg/kg body weight) was started.

At follow up examination four weeks later both patients complained of muscle pain and moderate weakness, which had developed a few days after treatment began. There was no history of excessive physical activity, intercurrent illness, additional drug or alcohol intake, or passing of dark red urine. One patient (case 1) had muscle tenderness on palpation of both thighs. The other (case 2) had tenderness on palpation of both shoulders and arms and moderate weakness of deltoid muscles without wasting. Complete blood counts and results of biochemical tests were normal. In case 1 creatine kinase activity was 918 IU/l (normal ≤203 IU/l) and aldolase activity was 8·8 IU/l (normal ≤7·6 IU/l). In case 2 muscle enzyme activities were normal. Electrodiagnostic studies showed normal motor and sensory nerve conduction velocities in both patients. Needle electromyography disclosed the presence of short duration and low amplitude action potentials, mainly in proximal muscles—the so called "myopathic pattern."

Isotretinoin was discontinued and during the next few days muscle pain gradually abated. At follow up examination one month later both patients had normal strength, muscle enzyme activities, and needle electromyograms.



(*a*) Several elliptical bodies composed of parallel bands are seen between normal muscle fibrils (arrow heads). The bodies seem to impinge on irregular Z bands (arrow), ×18 000. (*b*) Myoneural junction. Only primary clefts are seen in the folded sarcolemma. A large vacuole (V) is present in the nerve terminal, ×24 000.

PATHOLOGICAL FINDINGS

A biopsy sample of deltoid muscle was obtained in case 2. Light microscopy showed nothing abnormal except for slight variation in the size of muscle fibres. Electron microscopy showed elongated, elliptical, non-membrane bound bodies between the muscle fibrils. They were composed of parallel alternating bands 30 nm wide and had a diameter of 0·2 μm and length of 4-5 μm. They did not seem to be related to any cytoplasmic organelles, although they appeared to impinge on altered irregular Z bands (figure (*a*)).

Severe changes were noted in the myoneural junction. The folded sarcolemma contained only primary clefts. The nerve terminal appeared atrophic with abundant organelles and myelin figures and lacked synaptic vesicles. A large empty vacuole was seen within the Schwann cell cytoplasm impinging on the nerve terminal (figure (*b*)).

Comment

Both patients developed reversible muscle damage during treatment with isotretinoin. The findings on electron microscopy in case 2 are unique and

indicate damage to the muscle and myoneural junction. Such changes do not occur in primary muscle disorders, denervation atrophy, or drug toxicity.[2] Similar changes at the myoneural junction have, however, been reported in Becker's type of progressive muscular dystrophy.[3] In the absence of other factors known to precipitate muscle damage our data indicate that isotretinoin may induce reversible damage to skeletal muscle. Since there were no symptoms or signs of damage to the myoneural junction we refrained from performing a study of "jitter" or repetitive nerve stimulation.

We cannot offer an adequate explanation for our findings, although muscle pain and stiffness are features of chronic vitamin A toxicity.[4] A recent experiment showed that retinoic acid given in large doses to pregnant mice modified the phenotype expression of developing muscles in the fetus and increased creatine kinase activity.[5]

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Fish consumption and mortality from coronary heart disease

An inverse relation between consumption of fish and mortality from coronary heart disease has been found in some recent studies[1,2] but not in others.[3,4] In a 14 year follow up of 10 966 subjects in Sweden we studied the association between fish consumption and mortality from myocardial infarction and from coronary heart disease (including myocardial infarction).

Subjects, methods, and results

Information on current dietary habits, including fish consumption, was obtained by a self administered questionnaire in 1967-8 from 15 864 (75%) of the 21 152 subjects in the population based register of twins born in Sweden from 1886 to 1925. Each subject's average fish consumption in 1967 was related to his or her total intake of food and classified as high, moderate, low, or no fish consumption. Information on previous cardiovascular symptoms, including angina and myocardial infarction, was also obtained, and all subjects who reported such symptoms were excluded from the study. A link with the records of the Swedish National Cause of Death Register provided information on the year and cause of death for those among the remaining 10 966 subjects who died during 1969-82. The number of deaths from myocardial infarction and from coronary heart disease was related to the number of person years at risk during the period of observation. Relative risks for different levels of fish consumption were calculated using people who consumed little or no fish as the reference group. Differences in age and sex distribution were accounted for.[5] The results in the table show a dose response relation, with the lowest risk for those who had high fish consumption. Sex specific relative risks showed a similar pattern for men and women. Further adjustment was made for smoking habits, relative weight, marital state, geographical region, and degree of urbanisation (information obtained from the previously mentioned questionnaire in 1967-8), and for a history of hypertension (information obtained from a questionnaire in 1963). These adjustments, however, had little or no effect on the relative risks shown in the table.

Comment

The classification into high, moderate, low, or no fish consumption was peformed in 1967-8—that is, before the observation period. There were few subjects who never consumed fish, and we therefore had to include subjects with low fish consumption in the "unexposed" group. This may have led to an underestimation of the strength of the inverse relation between fish consumption and death from myocardial infarction and coronary heart disease. Similarly, the high levels of fish consumption in some earlier studies may account for the apparent lack of effect in these studies.

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Relative risks of death from coronary heart disease and myocardial infarction in relation to fish consumption of 10 966 subjects

Fish consumption	No of person years at risk	Coronary heart disease: No of deaths	Coronary heart disease: Relative risk* (90% confidence intervals)	Myocardial infarction: No of deaths	Myocardial infarction: Relative risk* (90% confidence intervals)
High	12 315	69	0·85 (0·69 to 1·06)	28	0·70 (0·50 to 0·98)
Moderate	70 848	373	0·94 (0·83 to 1·06)	184	0·91 (0·76 to 1·08)
Low	57 084	358	1·00	183	1·00

*Adjusted for age and sex.