collagen were detected in one of thirteen patients with sudden deafness and two of ninety-one healthy individuals.

The low positivity of type II collagen antibodies in patients with inner ear disease is not consistent with an autoimmune response against a_1(II) chains of type II collagen, which have a molecular mass of about 95 kDa. Additionally, the 68 kDa antigen of the inner ear might be more important in autoimmune sensorineural hearing loss.[7] The discrepancies between our results and those of Helfgott et al might represent differences in patient populations, and they point to a need for the collaborative exchange of serum samples between laboratories investigating the cause of sensorineural hearing loss.

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1. Hughes GB, Kinney SE, Barna BP, Calabese LH. Practical versus theoretical management of autoimmune inner ear disease. *Laryngoscope* 1984; **94:** 758–67.
2. Helfgott SM, Moscicski RA, San Martin J, et al. Correlation between antibodies to type II collagen and treatment outcome in bilateral progressive sensorineural hearing loss. *Lancet* 1991; **337:** 387–89.
3. Kirk AP, O'Hara BP, Mageed RAK, et al. Pepsinogen: an immunoglobulin binding artifact in 'collagen' preparations. *Clin Exp Immunol* 1986; **65:** 671–78.
4. O'Hara BP, Pyle J, McCarthy D, Archer JR. Binding of monomeric and aggregated immunoglobulins to enzymes: a source of artifact in antibody assay. *J Immunol Methods* 1989, **116:** 175–79.
5. Fujii K, Tsuji M, Murota K, et al. An improved enzyme-linked immunosorbent assay of anti-collagen antibodies in human serum. *J Immunol Methods* 1989; **124:** 63–70.
6. Terato K, Shimozuru Y, Katayama K, et al. Specificity of antibodies to type II collagen in rheumatoid arthritis. *Arthritis Rheum* 1990; **33:** 1493–500.
7. Harris JP, Sharp PA. Inner ear autoantibodies in patients with rapidly progressive sensorineural hearing loss. *Laryngoscope* 1990; **100:** 516–24.

Deafness after meningococcal meningitis

SIR,—Dr Mayatepek and colleagues (Nov 23, p 1331) reported a lower prevalence of deafness after meningitis due to *Neisseria meningitidis* serogroup B (3·3%) than when unusual serogroups were cultured (20%). Dr Moss (Dec 21/28, p 1602), however, did not find a significant difference in the frequency of deafness between children with meningococcal meningitis (5%) and controls (3%). We report here the findings of a retrospective study.[1]

Since 1959, strains and samples of cerebrospinal fluid (CSF) from patients with meningococcal disease in the Netherlands have been collected and investigated at the Netherlands Reference Laboratory for Bacterial Meningitis.[2] We examined the medical histories of 1221 patients (1959–83).[1] 62 patients (5%) died and 91 (8%) of the 1159 survivors had sequelae, 37 (3·2%) of whom had loss of hearing (table). Loss of hearing was seen less often in group B disease (14/744, 2%; 95% confidence interval [CI] 1·0–3·1%) than in all other groups (23/415; 5·5%; 95% CI 3·5–8·2%). CSF values (day of admission) in patients with group B disease were consistent with a lesser degree of inflammation (eg, lower white cell count and protein content) than were those with group A or C disease, whereas the duration of symptoms before admission was much the same in all groups[3].

Although in this study the proportion of patients with loss of hearing was low (probably because of missing data) there is no reason to suppose that the serogroup distribution differed among patients whose data were not available. Our results indicate that group B disease causes less inflammation and less hearing loss than that due to the other groups. This finding may arise because the immune system reacts less to the group B capsular polysaccharide, which is immunochemically identical to a fetal brain glycopeptide.[4] This is also shown by the low immunogenicity of this polysaccharide, which hinders the development of an effective vaccine against *N meningitidis* serogroup B. Other sequelae were evenly distributed among the serogroups. Why are unusual meningococcal serogroups associated with hearing loss more frequently (24% in our study) than common serogroups? There may be immunological reasons, since many patients with disease due to the uncommon groups have a complement deficiency.[5]

SEQUELAE AFTER MENINGOCOCCAL DISEASE IN THE NETHERLANDS (1959–83) ACCORDING TO SEROGROUP

Serogroup	No of survivors	Sequelae *(%)*	Hearing loss *(%)*
A	172	17 *(10)*	9 *(5)*
B	744	54 *(7)*	14 *(2)*
C	199	13 *(7)*	8 *(4)*
W135	27	2 *(7)*	2 *(7)*
Others*	17	5 *(29)*	4 *(24)*

*X (n = 3), Y (9), Z (1), non-groupable (4)

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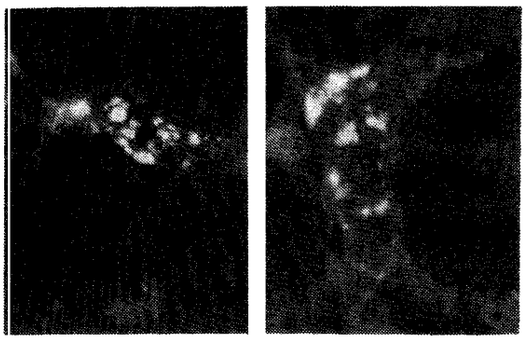
1. Spanjaard L, Bol P, De Marie S, Zanen HC. Association of meningococcal serogroups with the course of disease in the Netherlands, 1959–83. *Bull World Health Organ* 1987; **65:** 861–68.
2. Netherlands Reference Laboratory for Bacterial Meningitis (RIVM/UvA). Bacterial meningitis in the Netherlands; annual report 1990. Amsterdam: University of Amsterdam, 1991.
3. Spanjaard L. Epidemiology of bacterial meningitis in the Netherlands; volume 1. Chapter 8. Thesis. Amsterdam: University of Amsterdam, 1986.
4. Finne J, Leinonen M, Mäkelä PH. Antigenic similarities between brain components and bacteria causing meningitis; implications for vaccine development and pathogenesis. *Lancet* 1983; ii: 355–57.
5 Fijen CAP, Kuijper ED, Hannema AD, Sjoholm AG, Van Putten JPM. Complement deficiencies in patients over ten years old with meningococcal disease due to uncommon serogroups. *Lancet* 1989, ii: 585–88.

β-amyloid protein immunoreactivity in muscle of patients with inclusion-body myositis

SIR,—Inclusion-body myositis (IBM) is a usually sporadic progressive myopathy of unknown cause and pathogenesis.[1] It has clinical and pathological similarities to polymyositis, but is either not responsive, or only moderately so, to immunosuppressive treatment. Light-microscopic features of muscle-biopsy specimens include mononuclear inflammatory cells varying from abundant to none, atrophic muscle fibres, and muscle fibres with rimmed vacuoles that contain characteristic cytoplasmic tubulofilaments (CTFs) identified by electronmicroscopy.[2] We have shown that vacuolated muscle fibres contain strong ubiquitin immunoreactivity, which by immunoelectronmicroscopy was localised to CTFs.[3] Vacuoles also show Congo-red positivity, indicating amyloid,[4] but the type of amyloid protein has not been identified.

We report an investigation of 10 patients (aged 42-74, median 64) with inclusion-body myositis, including 1 hereditary case, and 14 control patients (aged 5-79, median 60), including 7 with polymyositis, 1 Duchenne muscular dystrophy, 4 amyotrophic lateral sclerosis, and 2 normal muscle. Vacuolated muscle fibres contained strong accumulation of β-amyloid protein (β-AP) within the vacuoles and sometimes in vacuole-free cytoplasm (figure). β-AP was identified by immunocytochemical staining with a well-characterised monoclonal antibody G-OP-1 directed against sequence 8–17 of a synthetic β-AP.[5] Omission of the primary antibody or replacing it with non-immune serum resulted in negative staining. With light microscopy, β-AP immunoreactivity closely co-localised with ubiquitin immunoreactivity. The amyloid inclusions were crystal-violet positive (metachromatic red) in all patients with sporadic disease, but not in the patient with hereditary disease. None of the muscle biopsy specimens from controls had β-AP-positive inclusions characteristic of inclusion-body myositis.

β-AP was discovered in and first sequenced from the amyloid fibrils in blood-vessels of patients with Alzheimer's disease,[6] and it has received considerable attention in the pathogenesis of this disease.[7] In brain of patients with Alzheimer's disease, β-AP immunoreactivity is present both in the amyloid fibrils (presumably β-pleated sheets), and located in blood-vessels and cores of senile plaques, as well as in non-fibrillar Congo-red-negative diffuse plaques, whereas ubiquitin immunoreactivity is seen at both locations.



Immunofluorescent staining of muscle-biopsy specimen from patient with inclusion-body myositis.

Transverse sections, showing positive β-amyloid protein deposits (white regions) in two abnormal muscle fibres Muscle fibre on left is more atrophic and vacuolated than that on right. Left × 1281, right × 1094, reduced by a factor of 1·4.

Previously, β-AP had not been localised in human muscle. The deposits of β-AP we describe in muscle-biopsy specimens from patients with inclusion-body myositis and the co-localisation with ubiquitin raise the possibility that β-AP deposits in muscle in inclusion-body myositis, and the brain findings in Alzheimer's disease may follow similar cellular events. The easily accessible muscle tissue may provide a good source for future molecular studies of β-AP to help to elucidate the pathogenesis of these two diseases.

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1. Dalakas MC Polymyositis, dermatomyositis and inclusion body myositis. *N Engl J Med* 1991; **325:** 1487–98.
2. Carpenter S, Karpati G, Heller I, Eisen A. Inclusion-body myositis: a distinct variety of idiopathic inflammatory myopathy. *Neurology* 1978; **28:** 8–17.
3. Askanas V, Serdaroglu P, Engel WK, Alvarez RB. Immunocytochemical localization of ubiquitin in muscle biopsies of patients with inclusion-body myositis and oculopharyngeal muscular dystrophy. *Neurosci Lett* 1991; **130:** 73–76.
4. Mendell JR, Sahenk Z, Gales T, Paul L. Amyloid filaments in inclusion body myositis. *Arch Neurol* 1991; **48:** 1229–34.
5 Wong CW, Quaranta V, Glenner GG. Neuritic plaques and cerebrovascular amyloid in Alzheimer's disease are antigenically related. *Proc Natl Acad Sci USA* 1985; **82:** 8729–32.
6. Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characteristics of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun* 1984; **120:** 885–90.
7 Yankner BA, Mesulam MM. β-amyloid and the pathogenesis of Alzheimer's disease. *N Engl J Med* 1991; **325:** 1849–57.

Reduced plasma L-arginine in hypercholesterolaemia

SIR,—L-arginine is the precursor for nitric oxide (NO) synthase in vascular endothelial cells,[1] and NO is an important regulator of vascular tone in man.[2] Hypercholesterolaemia impairs endothelial function—manifested as an attenuation of endothelial-dependent relaxation—before the formation of artherosclerotic lesions.[3-5] Experimental[6] and clinical[7] data have shown that impaired endothelial function in hypercholesterolaemia subjects could be corrected by L-arginine. This dysfunction might be due to substrate (L-arginine) deficiency, impairment of NO production or release, or inactivation of L-arginine.

To test the first hypothesis, we have examined in a prospective age-matched study plasma L-arginine concentrations in 13 patients with normal serum cholesterol and low-density lipoprotein (LDL) (group I), and in 13 patients with hypercholesterolaemia type IIa (group II). In group I, cholesterol was less than 220 mg/dl (mean 182, SD 22) and LDL was less than 140 mg/dl (123, 14), and patients were aged 30–76 years (mean 56, SD 13). In group II, cholesterol was over 270 mg/dl (mean 301, SD 27), and LDL was over 180 mg/dl (220, 25), and patients were aged 43–76 years (56, 10). Exclusion criteria were severe, systemic, or infectious diseases and disorders of the kidney and liver. None of the patients with hypercholesterolaemia had received lipid-lowering therapy in the 6 months before this study. The diagnoses of group I and II, respectively, were coronary artery disease (9/9), dilated cardiomyopathy (1/0), valvular heart disease (1/2), essential hypertension (2/2), peripheral vascular disease (1/2), and diabetes mellitus (2/3). Drug treatment was similar in the two groups. Blood samples were taken under standardised conditions—at 0800 h after 15 min rest, in the supine position, and 12 h after the last meal. L-arginine plasma concentrations were measured by high-performance liquid chromatography. Double control measurements showed an accuracy of 4·2% (SD 3). In patients with hypercholesterolaemia, L-arginine plasma values were significantly lower than in age-matched patients with normal cholesterol: (mean [SD]) 78·2 (21) *vs* 111·2 (22·8) μmol/l; $p < 0.001$).

As far as we are aware there are no other reports of reduced plasma L-arginine in patients with hypercholesterolaemia. These data suggest that impairment of endothelium-dependent relaxation in patients with hypercholesterolaemia may be, in part, due to a deficiency of L-arginine, the precursor of NO. The underlying mechanisms for reduced L-arginine remain to be elucidated. However, hypercholesterolaemia might be associated with diminished dietary L-arginine uptake (ie, food rich in lipids may contain less L-arginine) or altered L-arginine metabolism, such as increased arginase activity in the liver. If our findings are confirmed by investigations in a large patient population, L-arginine supplements may indeed represent a useful adjunctive and preventive treatment in patients with hypercholesterolaemia.

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1. Palmer RMJ, Ashton DS, Moncada S. Vascular endothelial cells synthesise nitric oxide from L-arginine. *Nature* 1988, **333:** 664–66.
2. Vallance P, Collier J, Moncada S. Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. *Lancet* 1989; ii: 997–1000.
3. Cohen RA, Zitnay KM, Haudenschild CC, Cunningham LD. Loss of selective endothelial cell vasoactive functions caused by hypercholesterolemia in pig coronary arteries. *Circ Res* 1988, **63:** 903–10.
4. Drexler H, Zeiher AM. Endothelial function in human coronary arteries in vivo. Focus on hypercholesterolemia. *Hypertension* 1991; **18** (suppl II): I–10.
5. Zeiher AM, Drexler H, Wollschlaeger H, Just H. Modulation of coronary vasomotor tone in humans: progressive endothelial dysfunction with different early stages of coronary atherosclerosis. *Circulation* 1991; **83:** 391–401.
6. Cooke JP, Andon NA, Girerd XJ, Hirsch AT, Creager MA. Arginine restores cholinergic relaxation of hypercholesterolemic rabbit thoracic aorta. *Circulation* 1991; **83:** 1057–62.
7. Drexler H, Zeiher AM, Meinzer K, Just H. Correction of endothelial dysfunction in coronary microcirculation of hypercholesterolaemic patients by L-arginine. *Lancet* 1991; **338:** 1546–60.

The J-curve hypothesis

SIR,—Dr Cruickshank (Jan 18, p 187) reminds us that, despite the stake driven through its heart by your Nov 23 editorial (p 1299), the J-curve hypothesis continues to stalk during dark moonless nights. But in what guise?

Initially, we were warned that reduction in blood pressure might be hazardous but only in hypertensive patients with pre-existing coronary heart disease; normotensive patients would be spared.[1] Most recently, we find that even subjects who had mostly never been hypertensive let alone treated are at risk.[2] Few would disagree that there must be a J-relation between diastolic blood pressure and coronary heart disease events. The critical question is, what is the level of the J-point? Here too, the goalposts are shifting; first 85–90 mm Hg,[1] now 75–79 mm Hg.[2] Is it time to lower the limit further?

In studies of left ventricular dysfunction (SOLVD), patients with symptomatic left ventricular (LV) dysfunction (heart failure) and symptomless LV dysfunction were randomised to treatment with the angiotensin-converting-enzyme (ACE) inhibitor enalapril or matching placebo.[3-6] Most patients enrolled had LV dysfunction due to coronary artery disease (usually previous myocardial infarction) and those with heart failure had fairly low arterial pressures (mean diastolic pressure 77 mm Hg).[3-6] Despite receiving