GIANT CELL ARTERITIS -
IMMUNOPATHOLOGY, LONG-TERM CORTICOSTEROID TREATMENT AND MORTALITY

by

Rune Andersson

Göteborg 1988

ERRATA

Andersson R. Giant cell arteritis-immunopathology, long-term corticosteroid treatment and mortality.

Thesis:

Page 11, line 5: .. nine women and two men.., should be..eight women and three men..
Page 28, line 9 from below: ..22.., should be..16..
Page 38, reference 53: ..even.., should be..seven..

Paper II

Page 6, table I, patient no 1: ..F.., should be..M..
Page 9, legend to figure 2: ..a.., should be..b..and..b.., should be..a..

Paper III

Page 467, table II, Glaucoma: ..3.., should be..8..
Page 468, Discussion line 10: ..that.. should be..this..

ADDENDUM

Paper II accepted for publication in Clinical and Experimental Immunology 1988.

GIANT CELL ARTERITIS -

IMMUNOPATHOLOGY, LONG-TERM CORTICOSTEROID TREATMENT AND MORTALITY

AKADEMISK AVHANDLING

som för avläggande av doktorsexamen i medicinsk vetenskap vid Göteborgs Universitet kommer att offentligen försvaras i föreläsningssalen, Infektionskliniken, Östra sjukhuset

fredagen den 25 mars 1988 kl 13.00
av
Rune Andersson
leg läk

Avhandlingen är baserad på följande arbeten:

I Andersson R, Jonsson R, Tarkowski A, Bengtsson B Å, Malmvall B E. T-cell subsets and expression of immunological activation markers in the arterial walls of patients with giant cell arteritis. Ann Rheum Dis 1987;46(12):915-23.

II Andersson R, Hansson G K, Söderström T, Jonsson R, Bengtsson B Å, Nordborg E. HLA-DR expression in the vascular lesion and circulating T lymphocytes of patients with giant cell arteritis. Submitted.

III Andersson R, Malmvall B E, Bengtsson B Å. Long-term corticosteroid treatment in giant cell arteritis. Acta Med Scand 1986; 220:465-9.

IV Andersson R, Malmvall B E, Bengtsson B Å. Long-term survival in giant cell arteritis including temporal arteritis and polymyalgia rheumatica. Acta Med Scand 1986; 220:361-4.

V Säve-Söderbergh J, Malmvall B E, Andersson R, Bengtsson B Å. Giant cell arteritis as a cause of death - report of nine cases. JAMA 1986; 255(4):493-6.

Göteborg 1988

GIANT CELL ARTERITIS - IMMUNOPATHOLOGY, LONG-TERM CORTICOSTEROID TREATMENT AND MORTALITY.

Rune Andersson, Department of Infectious Diseases, University of Göteborg, Östra Hospital, S-416 85 Göteborg, Sweden.

ABSTRACT

Giant cell arteritis (GCA) is a disease affecting medium-sized and large arteries in middle-aged or older persons. One purpose of this thesis was to describe the phenotypes of mononuclear cells infiltrating the temporal arteries of GCA patients. The expression of immunological activation markers on these cells and on vascular smooth muscle cells was also studied. The mononuclear cell infiltration was mainly composed of T-helper lymphocytes (CD4) and macrophages. About one-fourth of the infiltrating T lymphocytes expressed the MHC class II antigen HLA-DR, probably indicating immunological activation. Arterial smooth muscle cells did not express HLA-DR antigen. For comparison with these findings, the phenotypes of circulating T lymphocytes were studied in patients with GCA before and after 6-10 days of prednisolone treatment. The proportions of T lymphocytes, T-helper/inducer and T-suppressor/cytotoxic cells before treatment did not deviate from those in normal individuals. On average, six per cent of the circulating T lymphocytes expressed the HLA-DR antigen. The number of T-helper cells expressing HLA-DR and IL 2 receptor was not changed by the treatment given.

A second purpose of this thesis was to describe the morbidity and mortality in GCA patients receiving long-term corticosteroid treatment. A follow-up investigation of 90 patients with GCA was performed 11.3 years (median period) after diagnosis.The median duration of corticosteroid treatment was 5.5 and 2.3 years, respectively, for women and men. The incidences of diseases possibly related to corticosteroid treatment, such as diabetes mellitus, hip fractures or peptic ulcer, were not increased in the GCA patients as compared to the general population. Furthermore, these treated patients showed no increase in overall mortality or mortality from vascular diseases. However, GCA can be a threat to life due to engagement of cerebral and coronary arteries as well as of the aorta. This is seen in the initial phase of the disease and during insufficient corticosteroid treatment, which is illustrated by nine fatal cases, reported in detail.

The observations suggest that cell-mediated immunological mechanisms are involved in the pathogenesis of GCA and that long-term corticosteroid treatment is safe, effectively relieves symptoms, and prevents vascular complications otherwise associated with the disease.

Key words: prognosis, mortality, corticosteroids, immunopathology, T lymphocytes, HLA-DR,smooth muscle cells, myocardial infarction, cerebral infarction,aortic aneurysm.

ISBN 91-7900-410-5

pp 44

From the Department of Infectious Diseases
University of Göteborg, Göteborg, Sweden

GIANT CELL ARTERITIS -
IMMUNOPATHOLOGY, LONG-TERM CORTICOSTEROID TREATMENT AND MORTALITY

by

Rune Andersson

Göteborg 1988

GIANT CELL ARTERITIS - IMMUNOPATHOLOGY, LONG-TERM CORTICOSTEROID TREATMENT AND MORTALITY.

Rune Andersson, Department of Infectious Diseases, University of Göteborg, Östra Hospital, S-416 85 Göteborg, Sweden.

ABSTRACT

Giant cell arteritis (GCA) is a disease affecting medium-sized and large arteries in middle-aged or older persons. One purpose of this thesis was to describe the phenotypes of mononuclear cells infiltrating the temporal arteries of GCA patients. The expression of immunological activation markers on these cells and on vascular smooth muscle cells was also studied. The mononuclear cell infiltration was mainly composed of T-helper lymphocytes (CD4) and macrophages. About one-fourth of the infiltrating T lymphocytes expressed the MHC class II antigen HLA-DR, probably indicating immunological activation. Arterial smooth muscle cells did not express HLA-DR antigen. For comparison with these findings, the phenotypes of circulating T lymphocytes were studied in patients with GCA before and after 6-10 days of prednisolone treatment. The proportions of T lymphocytes, T-helper/inducer and T-suppressor/cytotoxic cells before treatment did not deviate from those in normal individuals. On average, six per cent of the circulating T lymphocytes expressed the HLA-DR antigen. The number of T-helper cells expressing HLA-DR and IL 2 receptor was not changed by the treatment given.

A second purpose of this thesis was to describe the morbidity and mortality in GCA patients receiving long-term corticosteroid treatment. A follow-up investigation of 90 patients with GCA was performed 11.3 years (median period) after diagnosis.The median duration of corticosteroid treatment was 5.5 and 2.3 years, respectively, for women and men. The incidences of diseases possibly related to corticosteroid treatment, such as diabetes mellitus, hip fractures or peptic ulcer, were not increased in the GCA patients as compared to the general population. Furthermore, these treated patients showed no increase in overall mortality or mortality from vascular diseases. However, GCA can be a threat to life due to engagement of cerebral and coronary arteries as well as of the aorta. This is seen in the initial phase of the disease and during insufficient corticosteroid treatment, which is illustrated by nine fatal cases, reported in detail.

The observations suggest that cell-mediated immunological mechanisms are involved in the pathogenesis of GCA and that long-term corticosteroid treatment is safe, effectively relieves symptoms, and prevents vascular complications otherwise associated with the disease.

Key words: prognosis, mortality, corticosteroids, immunopathology, T lymphocytes, HLA-DR,smooth muscle cells, myocardial infarction, cerebral infarction,aortic aneurysm.

ISBN 91-7900-410-5

pp 44

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I Andersson R, Jonsson R, Tarkowski A, Bengtsson B Å, Malmvall B E. T-cell subsets and expression of immunological activation markers in the arterial walls of patients with giant cell arteritis. Ann Rheum Dis 1987;46(12):915-23.

II Andersson R, Hansson G K, Söderström T, Jonsson R, Bengtsson B Å, Nordberg E. HLA-DR expression in the vascular lesion and circulating T lymphocytes of patients with giant cell arteritis. Submitted.

III Andersson R, Malmvall B E, Bengtsson B Å. Long-term corticosteroid treatment in giant cell arteritis. Acta Med Scand 1986; 220:465-9.

IV Andersson R, Malmvall B E, Bengtsson B Å. Long-term survival in giant cell arteritis including temporal arteritis and polymyalgia rheumatica. Acta Med Scand 1986; 220:361-4.

V Säve-Söderbergh J, Malmvall B E, Andersson R, Bengtsson B Å. Giant cell arteritis as a cause of death-report of nine cases. JAMA 1986; 255(4):493-6.

CONTENTS

ABBREVIATIONS

ESR	= Erythrocyte sedimentation rate
G	= General symptoms only in GCA
GCA	= Giant cell arteritis
IFL	= Immunofluorescence
IL 2	= Interleukin-2
MHC	= Major histocompatibility complex
MNC	= Mononuclear cells
NK-cells	= Natural killer cells
PMR	= Polymyalgia rheumatica
SMC	= Smooth muscle cells
T	= Temporal arteritis
TP	= Temporal arteritis + polymyalgia rheumatica

DEFINITIONS: Flare-up of the disease = symptoms of the disease that necessitate an increase in the dose of ongoing corticosteroid treatment.

Relapse of the disease = symptoms of the disease after withdrawal of treatment.

INTRODUCTION

Giant cell arteritis is a disease with inflammation in medium-sized and large arteries, mainly affecting persons over the age of 50 years. The annual overall incidence of the disease in Göteborg has been calculated to be 9.3 cases per 100,000 inhabitants, but in the ages over 50 years the incidence is 28.6 per 100,000 (11). The disease is about twice as common among women.

Up until the 1950s giant cell arteritis was usually divided into temporal arteritis and polymyalgia rheumatica. Porsman and Paulley then realised that the two conditions were clinically inseparable and merely two expressions of the same disease, including a more or less generalised arteritis (120,122). This has been confirmed by many authors during the last decades (1, 12, 34, 44, 63, 66, 78, 130, 140).
The name giant cell arteritis was first used by Gilmour in 1941 (40). In this thesis the term "giant cell arteritis" is used for the disease, including both temporal arteritis and polymyalgia rheumatica.

Histopathology

The histopathological picture of giant cell arteritis has been well known since the descriptions in the 1930s by Horton (52, 53) and by Gilmour in 1941 (40). The arterial wall presents an infiltration of mononuclear cells concentrated around the inner half of the media centering upon the fragmented internal elastic membrane. A more severe inflammation may continue throughout the outer half and adventitia as well. Giant cells are frequently but not always seen. Luminal constriction may occur in severe cases. Electron-microscopic examination of the arteries has confirmed the lightmicroscopic findings and has added information about the smooth muscle cells, demonstrating degenerative changes with swelling of the mitochondrias and vacuoles in the cytoplasma (123).

Pathogenesis

Many hypotheses concerning the pathogenesis of GCA have been presented since Hutchinson's suggestion in 1890 that the pressure from the hat may cause the disease (59). O'Brien thought infrared irradiation could cause the disease by transcutaneous damage to the elastin (108). The influenza-like onset of the disease has prompted a search for a viral aetiological agent. Hepatitis B as a trigger for PMR was suggested by Bacon (5) but other studies (19, 30, 85) have not confirmed the observation of an increased prevalence of

hepatitis B antibodies among GCA patients.

Among infectious diseases, long-lasting polymyalgia has been described in yersiniosis (112). Fessel (37) found that 46 per cent of patients with PMR or temporal arteritis had had significant contact with pet birds, particularly parakeets, compared to 26 per cent of controls, but later studies (111, 137) have not confirmed these results.

Degradation of elastic fibres in the arterial wall in GCA was observed in 1952 by Kimmelstiel and co-workers (71). The striking localisation of the inflammation around the internal elastic lamina has given rise to the theory of a reaction against elastin as the pathophysiological mechanism. If heterologous elastin is implanted in the subcutis or peritoneum of rats, the cellular infiltration begins with neutrophils, continues with lymphocytes, fibroblasts and macrophages and ends with the formation of giant cells (116). Further support is the finding of linear deposits of leukocyte elastase along the fragmented internal elastic membrane (136). However, no antielastin antibodies have been found in serum of GCA patients (57), and in electron-microscopic studies no signs of phagocytosis of elastin were observed (24, 119).
It is also possible that the observed histopathological changes reflect a non-specific reaction to injury, regardless of the cause of the disease. This hypothesis is supported by the finding of similar changes after experimental dilatation injury of the carotid arteries in rabbits (124).

Immunological features have been studied extensively in patients with GCA. Deposition in the arterial wall of immunoglobulin and complement in the majority of the patients has been found by some authors (84, 117, 127, 135, 136) but not by others (6, 25, 39, 123). Waaler and co-workers (135) demonstrated anti-immunoglobulin in the arterial wall. Increased levels of circulating immune complexes have been observed in some studies (14, 33, 115, 118, 143) but not in others (93).
Hazleman observed that lymphocytes from patients with PMR showed higher transformation responses to arterial antigens than lymphocytes from controls (49). This observation has, however, not been confirmed by others (93, 114, 146).
Further support for the involvement of immunological mechanisms in the pathogenesis of GCA was the finding of an increased prevalence of the major histocompatibility complex (MHC) antigens HLA-DR3, HLA-DR4 or HLA-DR5 (2, 7, 92) in patients with GCA. A high prevalence of these antigens is associated

with disorders that have an autoimmune basis (92).

Not until recently have techniques been developed that allow cellular interactions to be studied in situ. The development of the monoclonal antibodies which recognise functional subpopulations of lymphoid cells has been a major advance (79). During the last few years, a wide variety of monoclonal antibodies have become commercially available, giving us a new opportunity to characterise the cells in both tissue and blood. Regarding GCA, only a few previous studies have been published, with conflicting results (6, 14, 23, 25, 31).

Treatment of GCA

Corticosteroid treatment in GCA was first reported in 1950 (129). An excellent therapeutic response was soon recognised and found to be an almost diagnostic feature. The duration of treatment and the risk of corticosteroid side effects has been evaluated in several reports (3, 9, 10, 26, 27, 36, 50, 58, 76, 130), most of them based on relatively small patient groups or a short time of observation. The reported average duration of the treatment ranges from seven months (58) to six years (36). The most common corticosteroid side effects suggested are diabetes mellitus, hip fractures, vertebral crush fractures, peptic ulcer and cataract, but the prevalences of these complications vary widely in the available studies.

Mortality in GCA

GCA is a generalised arteritis involving large and medium-sized arteries. Due to engagement of the cerebral and coronary arteries and the aorta, the disease can be a threat to life. However, only a few fatal cases are reported in the literature and most clinicians are probably not aware that GCA can cause cerebral and myocardial infarction as well as aortic aneurysms.

In most hospitals, microscopic examination of the coronary and cerebral arteries is not routinely performed at autopsies of patients with fatal myocardial and cerebral infarctions. Nor is the aortic wall studied in detail in most patients with ruptured aneurysms. The real prevalence of fatal GCA is thus not known, but in most studies the overall mortality rates among corticosteroid-treated patients are similar to those in the general population (26, 41, 42, 47, 58, 64, 77).

AIMS OF THE STUDY

The main purposes of this study of GCA patients were:

- To characterise the phenotypes of infiltrating mononuclear cells in the temporal arteries of patients with GCA and to evaluate the expression of immunological activation markers on these cells.

- To ascertain whether there is immunohistological evidence for engagement of the smooth muscle cells in the inflammatory process in the temporal arteries.

- To determine the prevalence of immunological activation markers on T lymphocytes in the blood.

- To evaluate the long-term mortality and morbidity in corticosteroid-treated patients.

- To describe the occurrence of fatal GCA in vital arteries.

PATIENTS AND METHODS

Patients

Altogether 138 patients with GCA were studied.

Ninety patients (68 women and 22 men) were diagnosed as having GCA between 1968 and 1975 at the Department of Medicine III, Sahlgrenska Hospital, and the Department of Infectious Diseases, Östra Hospital, Göteborg. Their mean age at diagnosis was 72 years (range 52-86 years). The results of a follow-up examination in 1979 have been presented in a thesis by Bengtsson and Malmvall in 1982 (13). A long-term follow-up investigation was performed between January and September 1985, resulting in papers III and IV. A median time of 11.3 years had then elapsed since diagnosis. All patients were traced and medical records of outpatient and hospital care were studied for all 90 patients. During the observation period, 43 patients died (28 women and 15 men). Their mean age at death was 82.5 years. The 47 patients alive at the time of follow-up had a mean age of 79.8 years. Forty-two of them were medically examined and questioned.

In papers I and II, thirteen women with histologically verified GCA were compared with six women with GCA but negative histological findings and seven patients (four women and three men) with other, unrelated, diseases. In paper II, the biopsies of the temporal arteries from an additional eleven patients (nine women and two men) with GCA were compared with biopsies from three women with unrelated diseases. In paper II, blood samples were obtained from a new patient group of six women and four men with GCA.

Nine patients with GCA as a cause of death were collected from the departments of pathology in Göteborg between 1978 and 1984 and are presented in paper V. One of the patients belonged to the series of 90 patients presented in papers III and IV.

The patients were divided into the following four clinical groups:

I. Temporal arteritis (T): patients with symptoms from the temporal region such as headache, scalp tenderness, jaw claudication and tenderness and swelling of the temporal artery.

II. Polymyalgia rheumatica (PMR): patients with proximal muscle symptoms of pain and morning stiffness without signs of inflammatory arthritis.

III. Temporal arteritis and polymyalgia rheumatica (TP): patients with both symptoms from the temporal area and polymyalgia rheumatica.

IV. General symptoms (G): patients with no clinical symptoms from the temporal region or proximal muscles but with constitutional symptoms such as fever, fatigue and malaise. All the patients in this group had a histologically proved arteritis.

Diagnostic criteria for GCA

Patients were diagnosed as having GCA if a temporal artery biopsy showed arteritis, characterised by the histological findings of interruption of the internal elastic membrane with infiltration of mononuclear cells in the arterial wall. Giant cells were often found but their presence was not required for diagnosis.

In patients with negative histological findings, the diagnosis of GCA was accepted if they fulfilled the following clinical criteria:

Pain and stiffness affecting at least two large groups of proximal muscles (i.e. neck, shoulders - upper arms, hips and thighs) with duration of symptoms of more than two weeks and without evidence of inflammatory arthritis.

Elevated erythrocyte sedimentation rate (ESR) above 40 mm/h and an age of 50 years or more.

No clinical or laboratory evidence of infection, malignant disease, rheumatoid arthritis, systemic lupus erythematosus or periarteritis nodosa.

A prompt and long-lasting relief of symptoms after institution of corticosteroid treatment.

Immunohistochemical methods

Temporal artery specimens were studied from altogether 40 patients. Twenty-one of the biopsies showed histological signs of GCA on examination by routine light microscopy. Nine patients had GCA according to clinical criteria but a negative biopsy. As controls, we used eleven biopsies from ten patients who proved to have other unrelated diseases.
The specimens were rapidly frozen and stored at -70°C.

Six-micron-thick serial sections from the arteries were prepared in a cryostat. They were then analysed either by immunoperoxidase (paper I) or double immunofluorescence (paper II) technique.

Antibodies

The following monoclonal antibodies were used (see also table I):

Anti-Leu 4 reacts with the T-cell antigen CD3, present on all T lymphocytes (56).

Anti-Leu 3a and 3b is directed against the CD4 antigen present on T-helper/inducer lymphocytes (81). In addition, some of the monocytes and macrophages may react weakly with the antibody (142).

Anti-Leu 2a is directed against the CD8 antigen present on the suppressor-/cytotoxic T-cell subset (81).

Table I. **Antibodies used in the immunohistochemical study of GCA**

Name	Specificity	Produced in	Supplier
Monoclonal antibodies			
Anti-Leu 4	CD3, all T lymphocytes	mouse	A
Anti-Leu 3a+b	CD4, T-helper/inducer lymphocytes, some macrophages and monocytes	mouse	A
Anti-Leu 2	CD8, T-cytotoxic/suppressor lymphocytes	mouse	A
Anti-Leu M3	CD14, monocytes and macrophages	mouse	A
Anti-Leu 12	CD19, all B lymphocytes	mouse	A
Anti-HLA-DR	MHC class II antigen HLA-DR	mouse	C
Anti-HLA-DR	-"-	-"-	E
YE2.36	-"-	rat	D
Anti-transferrin receptor	Transferrin receptor	mouse	A
Anti-Interleukin-2 receptor	CD25, interleukin-2 receptor	mouse	C
Polyclonal antibodies			
Anti-asialo GM1	Natural killer (NK) cells	rabbit	B
Anti-smooth muscle myosin	Heavy chain of smooth muscle myosin	rabbit	F

Suppliers:

A = Becton and Dickinson, Sunnyvale, CA, USA
B = Wako, Osaka, Japan
C = Dakopatts, Glostrup, Denmark
D = Sera-lab, Crawley-Down, Sussex, U.K.
E = Atlantic antibodies, Scarbourogh, Maine, USA
F = Dr BM Larson, Boston University, Mass. USA

Anti-Leu M3 is directed against the CD14 antigen. It labels monocytes and macrophages (29).

Anti-Leu 12 reacts with the CD19 antigen present on all B lymphocytes (98).

Anti-HLA-DR reacts with the MHC-class II antigen HLA-DR (4).

YE2.36 is directed against the HLA-DR antigen (18).

Anti-transferrin receptor The expression of the transferrin receptor has been found to correlate with the proliferative status in both normal and malignant mononuclear cell populations (134).

Anti-Interleukin-2 receptor reacts with the CD25 antigen that is associated with high affinity binding of interleukin-2. Interleukin-2 receptor expression is a prerequisite for subsequent IL 2 binding and activation of T-cells (82).

Two polyclonal antibodies were used (Table I):

Anti-smooth muscle myosin reacts with the smooth muscle specific form of the heavy chain of myosin (80).

Anti-asialo-GM1 identify the natural killer (NK)-cells (69).

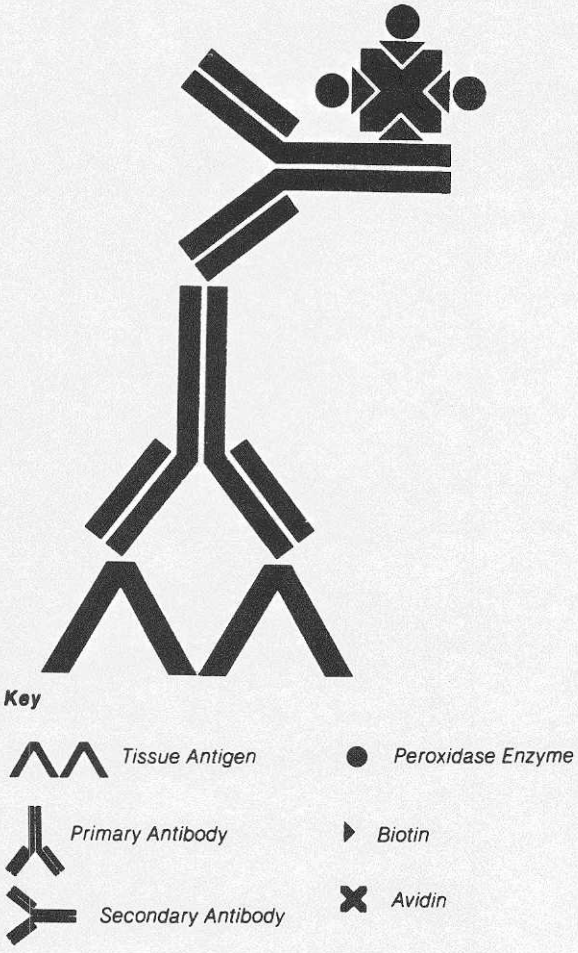
In the immunoperoxidase technique, the sections were incubated with the monoclonal antibodies using biotin-labelled species-specific anti-immunoglobulin as the secondary reagent. Binding of biotin-labelled antibodies was detected after incubation with avidin-biotin-peroxidase complexes (55) (Fig. 1) and subsequent use of H_2O_2 and a buffer containing 3-amino-9-ethylcarbazol. The sections were counterstained with Mayers' haematoxylin and studied under a light microscope.

Figure 1

Avidin-biotin-peroxidase complex

Reprinted with permission from

Bourne JA: Handbook of Immunoperoxidase staining methods. Dako corporation 1983.



In the double immunofluorescence technique, the cryostat sections were first incubated with monoclonal antibodies against HLA-DR, followed by species-specific biotinylated anti-IgG and FITC-streptavidin. They were then incubated with anti-myosin or Leu 4 and finally species-specific rhodamine-labelled anti-IgG. The sections were studied under a fluorescence microscope with interference filters for fluorescein and rhodamine.
All antibodies were used at optimal dilutions, which were determined by checkerboard titrations on peripheral blood smears, lymph nodes or atherosclerotic plaques.

A fluorescence-activated cell sorter (FACS) was used for study of the T-subsets and markers of immunological activation in peripheral blood.
The surface expression of antigens on peripheral blood lymphocytes was determined by quantitative two-colour analysis with a FACS tar (Becton-Dickinson, CA, USA). Forward (i.e. size) and right-angle (i.e. granulation) scatter gates were set on lymphocytes excluding monocytes and other leukocytes. Analysis was performed on 10 000 cells from unseparated heparinised blood using Fluorescein 5-Isothiocyanate (FITC) or R-Phyco-erythrin-conjugated monoclonal antibodies.

Statistics

The expected number of deaths in the GCA patients was calculated by adding mortality risk rates obtained from the official Swedish statistics (87) for each month of observation for each patient, until death or until January 1985. Death rates for vascular, malignant and infectious diseases were compared with data from official Swedish statistics (133). Statistical comparisons of observed and expected mortality were made by using significance limits for the Poisson distribution.
For calculation of the median duration of corticosteroid therapy we used a life-table method. For statistical comparisons, we used the univariate chi squares for log rank test (68).
For comparing the T-subsets in blood before and after treatment with prednisolone, we used Fischer's two-sided test for pair comparisons.

RESULTS AND DISCUSSION

Immunohistochemical findings (papers I and II)

Almost all the lymphocytes in the arteritic lesions of patients with giant cell arteritis expressed the T-cell phenotype. No or very few B-cells were found. In all patients, the T-helper/inducer (CD4)-subset dominated over the T-suppressor/cytotoxic (CD8)-subset. A low number of natural killer (NK) cells was detected in the arterial wall from most GCA patients and controls.

In all the biopsies with signs of arteritis, we also found an infiltration of macrophages. Usually, the number of macrophages was slightly lower than the number of lymphocytes. The mononuclear cells (MNC) in 11 out of the 13 positive biopsies showed staining for HLA-DR antigen using the immunoperoxidase technique. With the double immunofluorescence method, macrophages and lymphocytes expressing the HLA-DR antigen were found in 20 out of 21 positive biopsies. The relative number of infiltrating T-cells expressing the HLA-DR antigen was on average 28% (range 16-42%). In 6 out of the 11 control biopsies expression of HLA-DR antigen was infrequently observed.

Our findings are in agreement with those of Banks and co-workers (6), who observed a predominance of the T-helper/inducer subset and noted that the MNC expressed the HLA-DR antigen. In contrast, Chess and coworkers (25) found equal numbers of T-helper/inducer and T-suppressor/cytotoxic cells.

The human major histocompatibility complex (MHC)-class II antigens are HLA-DR, -DQ, and -DP (4). The class II antigens are involved in the presentation of antigens, and a foreign antigen is only recognised by the T-helper lymphocyte if it is presented together with the class II antigens on the surface of an antigen-presenting cell (for review see 113). The interaction between the class II antigens, foreign antigen and the T-helper lymphocyte leads to an immunological activation of the T lymphocyte, which then expresses the interleukin-2 receptor and produces interleukin 2 (IL 2), as well as other lymphokines. Among the activated T-helper lymphocytes, two subpopulations can be recognised: one that stimulates B lymphocytes to antibody production (103) and another one that induces cell-mediated immune responses (102).

HLA-DR antigens are constitutively expressed on mature B lymphocytes and a subpopulation of macrophages (60, review). The T lymphocytes, on the other hand, express HLA-DR antigens only in the activated state (60). The frequent

expression of HLA-DR antigens on the T lymphocytes in the arteritic lesions therefore indicates that immunological activation has taken place (94).

Further support for a local activation of the T-cells was the finding of interleukin-2 receptors on the lymphocytes in 6 out of 13 biopsies with signs of arteritis. The IL 2 receptor expression on the lymphocytes was not as frequent as the HLA-DR expression. The reason for this discrepancy is not known but the same pattern has been observed in other inflammatory lesions, such as salivary glands in sialoadenitis (67, 128) and synovial tissue in rheumatoid arthritis (20). The activated status of the T-cells was also demonstrated by the detection of transferrin receptors on lymphocytes in 7 out of 13 positive biopsies.

It remains to be established whether homing of activated T-cells into arteritic areas takes place or whether expression of HLA-DR antigen, IL 2 receptor and transferrin receptor is induced *in situ*.

Expression of HLA-DR can be induced in normally negative cells, e.g. on thyrocytes in Hashimoto's thyroiditis (62) and on glandular epithelial cells in Sjögren's syndrome (88). Such an abberant expression of HLA-DR on vascular smooth muscle cells has been reported both in studies on atherosclerosis in this laboratory (46, 65) and in vasculitis in the MRL/-lpr mouse model (105).
By means of the double-staining immunofluorescence technique, we stained the temporal artery biopsies in the patients with GCA for HLA-DR antigen and myosin. A strong staining for myosin, detecting the smooth muscle cells, was found in the arterial walls but without any concomitant staining for HLA-DR. The results indicate that the immunopathogenetic mechanisms are different in giant cell arteritis on the one hand and atherosclerosis and MRL/-lpr vasculitis on the other.

Our results suggest that a cell-mediated immune reaction, possibly against an autologous antigen, is occurring locally in the arteritic lesions of GCA. The observed HLA-DR expression in the arterial wall can be accounted for by the sum of macrophages and activated T-cells, the macrophages being the most probable antigen-presenting cells. What the antigen(s) may be is, however, still unknown, as are the factors initiating the process.

The immunohistochemical pattern, with a predominance of T-helper/inducer cells surrounding HLA-DR-expressing cells, represents a common immune

reaction in man and has been found in several different conditions, not only in diseases with a putative autoimmune pathogenesis, e.g. rheumatoid arthritis (89), Hashimoto's thyroiditis (62), sialadenitis (Sjögren's syndrome) (88, 128) and myositis (110), but also in synovitis due to trauma or crystals (89), osteoarthritis (90), thyrotoxicosis (62) and atherosclerosis (65).

Circulating T lymphocytes (paper II)

The proportions of T lymphocytes, T-helper/inducer and T-suppressor/cytotoxic cells were within the normal range in the blood from 10 patients with GCA before treatment with corticosteroids. The results are in agreement with those of Banks and co-workers (6) but in contradiction to previous reports of a selective decrease of T-suppressor/cytotoxic cells in GCA (14, 23, 31). The latter studies conflicting with our results were performed on separated mononuclear cells, which may cause changes of the T-cell ratios during preparation (61). In addition, all but Banks and coworkers (6) utilized manual reading by microscope, which may be a less sensitive method for detecting fluorescence.

In contrast to the high prevalence of HLA-DR expression on the T lymphocytes in arterial wall, only 2-14 per cent (mean 6%) of the T-helper/inducer cells and 0-10 per cent (mean 6%) of the T-suppressor/cytotoxic cells in the blood expressed the HLA-DR antigen. This is about the same as in healthy normal individuals with reported mean values for HLA-DR expression on T lymphocytes of 2.4-7.4% (21, 139, 145). As rheumatoid arthritis can be a differential diagnosis for GCA, it is of interest to note that the population of T-cells expressing HLA-DR exceeded 20% in one-third of the patients with rheumatoid arthritis (145).

All the patients were treated with prednisolone 30-50 mg daily and after 6-10 days we found a minor increase of the T-helper/inducer (CD4) subset from 0.5-2.3 (mean 1.3) x 10^9/l to 0.8-3.7 (mean 1.9) x 10^9/l. The increase was statistically significant ($p=0.04$). The number of T-suppressor/cytotoxic (CD8) cells was not changed. The CD4/CD8 ratio thus increased by on average 0.8 ($p=0.002$).

Corticosteroids are known to cause a transient lymphocytopenia (35, 48, 144), especially decrease of the T-helper cells (48). The lowest values of T-helper cells are seen about four hours after administration of cortisone, with a slight rebound increase after 24 hours (48). This can explain the

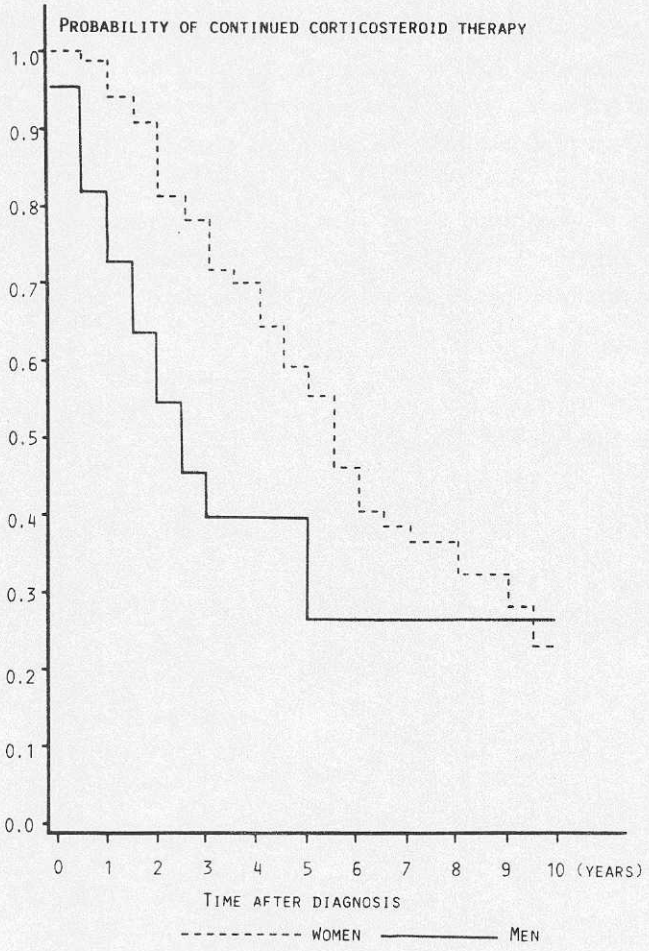
observed increase of T-helper cells in our patients, as the blood samples were obtained in the morning about 24 hours after the last prednisolone dose.

The absolute number of T-helper cells expressing HLA-DR antigen was not altered after 6-10 days of treatment with prednisolone. Interleukin-2 receptors were detected on 0-4 per cent (mean 1%) of the circulating T-helper cells before treatment, with no statistically significant changes after prednisolone was given.

Effects of long-term corticosteroid treatment (paper III)

Dosage and duration of corticosteroid treatment

Figure 2



Probability of continued corticosteroid therapy at different times after diagnosis in ninety patients with giant cell arteritis.

Ninety patients (68 women and 22 men) were followed up after a median time of 11.3 years from the time of diagnosis of GCA. All but one patient were treated with corticosteroids. The mean initial dose of prednisolone was 33.2 mg (range 0-60 mg). The median duration of treatment was estimated, by using the life-table method, to be 5 years (fig. 2).

Seventy-five per cent of the patients received treatment for two years or more and 23% for more than 10 years (Fig. 2).

Fifty per cent of the women were still on treatment at 5.5 years from diagnosis, compared to 2.3 years for the men (p=0.06)(Fig. 2). A shorter duration of treatment for men has also been observed by Chuang (26) and Ayoub (3).

No significant differences were found when the probability of continued corticosteroid therapy against time after diagnosis was compared for the four different clinical groups of GCA.

Figure 3 shows the prednisolone dosage 1-9 years after diagnosis. Sixty patients were alive after nine years. Fifteen of them (25%) were on treatment with 1.25 mg-10 mg prednisolone (median 5 mg) daily.

At the time of follow-up examination, 8 out of 47 surviving (17%) patients were on treatment with prednisolone. They had been treated for 5.2-11.7 (median 10.4) years. The prednisolone dose was 2.5-7.5 (median 5) mg daily.

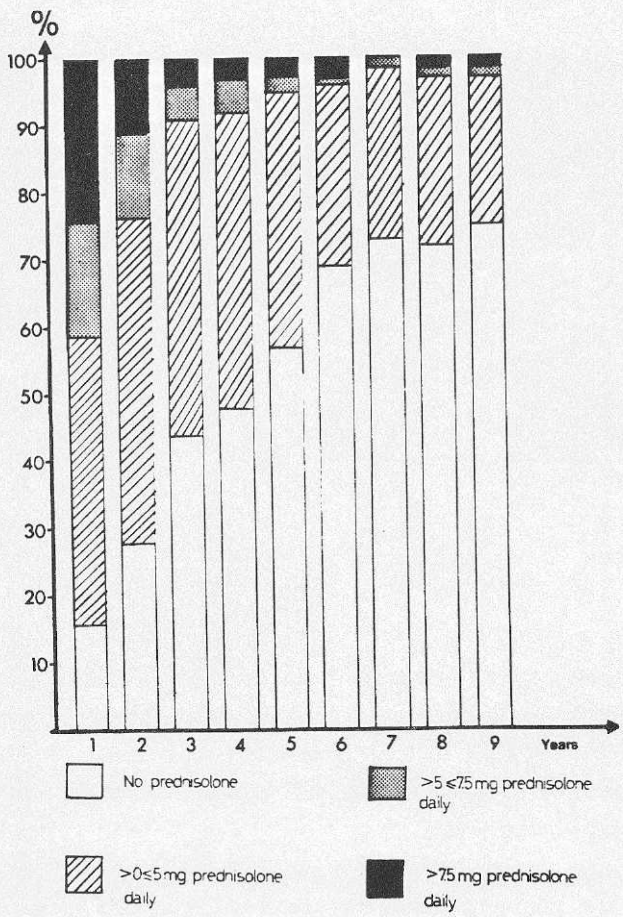


Figure 3

Percentage of GCA patients on different doses of prednisolone, surviving 1 - 9 years after diagnosis in a series of orginally ninety patients.

Of the 43 patients who died during the observation period, 19 were on corticosteroid treatment at the time of death 0.3-13.3 (median 5.1) years after diagnosis. The prednisolone dose ranged from 2.5 to 20 (median 5) mg daily.

The corticosteroid treatment makes the patients free from symptoms but no report suggests a shorter duration of the disease compared to untreated patients.

In reports from Minnesota, the median duration of the treatment was found to be only 7 months for temporal arteritis (58). Similar to us, Healey noted that 42% of the patients were still taking steroids after 5 years (50), and Fernandez-Herlihy registered a mean duration of corticosteroid treatment of 6 years (36). Ayoub reports a shorter median duration of treatment, 37 months (3) and Coomes observed that 84% of the patients still required steroids after 5 years (27).

These differences may be due to variations in sex distribution and to selection mechanisms in the countries and departments where the patients were collected. Our results are based upon a large patient group and a long duration of observation compared to the other studies. The patients were collected from the entire city of Göteborg without any obvious selection and the presented duration of GCA thus should represent a good estimate of the situation in the GCA-affected population. The duration of treatment observed by us differs from that described in many textbooks (8), which suggests that the needed duration of treatment usually is shorter.

Relapse of GCA

Forty-nine relapses were registered after 104 attempts to withdraw the corticosteroid treatment in 72 patients. This gives an overall relapse rate of 47%. The rate is about the same regardless of the time after diagnosis when the attempt to withdraw the treatment was made. Nor was there any difference in relapse rate between the polymyalgia rheumatica and temporal arteritis groups.

As demonstrated in table II, 46% of the relapses occurred within the first month and 67% within two months of the termination of treatment. Ninety-six per cent occurred during the first year.

In 15 out of the 90 patients, no relapses or flare-ups were registered.

Table II **Number of relapses in relation to time after withdrawal of corticosteroid treatment in 72 patients with GCA**

	Time after withdrawal (months)					
	≤1	>1≤2	>2≤6	>6≤12	>12	Total
Number of relapses	22 (46%)	10 (21%)	8 (17%)	6 (12%)	2 (4%)	48 (100%)

In other studies, the reported relapse rate after withdrawal of corticosteroids is 30 out of 72 (42%) (10), 13 out of 56 (23%) (34), 13 out of 37 (35%) (3) and no relapses (36). v. Knorring (76) observed that 26 out of 33 relapses (79%) occurred within one month and Fauchald (34) reported 7 out of 13 (54 %) relapses within three months after discontinuation of treatment.

The conclusion must be that it is very important to observe the patient carefully during the first year after termination of the treatment.

Flare-up of GCA during treatment

One hundred and fifteen flare-ups were registered in 48 patients. Forty-six per cent of them occurred within the first year of treatment. Thirteen per cent of the flair-ups were seen after more than five years and five per cent after more than seven years. Seventy-seven per cent of them were seen during treatment with 7.5 mg of prednisolone or less. The most common symptom of flare-ups was muscular discomfort, regardless of which clinical group the patient belonged to at the time of diagnosis.

Health condition of the patients at follow-up

Despite their high age (mean age 80 years) most patients were in excellent condition at the follow-up examination. About two-thirds coped with their activities of daily living without help. Thirteen per cent lived in institutions. Seventy-seven per cent read a daily newspaper.

Three of the patients were blind, but due to other diseases than GCA. None of the patients had any symptoms or laboratory values indicating ongoing relapse or flare-up of the disease.

Diseases diagnosed during the observation period

Table III **Number of patients with different diseases diagnosed after GCA in a series of orginally ninety patients with a median follow-up time of 11.3 years**

	N	Cause of death (N)
Malignant diseases	14	7
Aneurysm of the aorta	6	2
Myocardial infarction	13	6
Cerebrovascular infarction	19	6
Diabetes mellitus	10	1
Hip fractures	8	
Compression fractures of the spine	6	
Gastric or peptic ulcer	6	
Cataract	18	

The recorded diseases in our ninety patients with GCA, during a median follow-up period of eleven years, are listed in table III.

The morbidity from malignant diseases appeared to be as expected compared to the general population of the same age, which also has been reported by von Knorring (75) and Boesen (17).

Among the vascular diseases, we observed six cases of aneurysm of the aorta in our 90 patients (7%). The incidence of aortic aneurysms in Sweden is not known, but in a population study from Rochester, USA (99) the annual incidence of aortic aneurysms in 1971-80 between the ages of 70 and 79 years has been estimated to be 465 per 100 000 person-years for men and 115 per 100 000 person-years for women. With that incidence, only 2 cases of aortic aneurysms could be expected during the observation period in our patients. The incidence of aneurysms among GCA patients thus seems to be increased compared to the general population.
In an autopsy study, Östberg found aortic aneurysms in 11 out of 79 patients (14%) with GCA (147). Among the thoracic aortic aneurysms treated at a department of surgery, 5 out of 43 (12%) patients were found to have giant cell arteritis (131). The possibility of GCA should be considered in all cases of aortic aneurysms and microscopic examination is recommended on aortic specimens obtained during operation of aneurysms.

The incidences of myocardial infarction and cerebrovascular disease are high even in the general population of elderly persons and a minor increase in morbidity is difficult to detect. In a population study from Göteborg (83), nine per cent of the men and eight per cent of the women suffered non-fatal myocardial infarction between 70 and 75 years of age. A few case reports on non-fatal giant cell arteritis in the coronary arteries (100, 121), aorta (74, 95, 109, 126, 131) and cerebral arteries (32, 91, 101, 141) have been published but the prevalence of GCA in vital arteries is not known.

Corticosteroid side effects

In our 90 patients, we found 10 cases of diabetes mellitus during the median observation period of 11 years. A population study in Göteborg shows an annual incidence of diabetes mellitus of about 1% in men and women aged 70-80 years (S. Landahl, personal communication). The observed diabetes incidence in our patients thus does not seem to be higher than in the general population.

We found eight patients with fractures of the neck of the femur. Nilsson (107) reported an incidence of hip fractures in Stockholm in 1978 of 1,2 per cent for women and 0,7 per cent for men at ages between 75 and 79 years. The observed incidence of hip fractures in our patients is thus about the same as expected.

Compression fractures of the spine verified by X-ray and not known before treatment were found in 6 of the patients (all women) when even minor compressions were included. However, X-ray of the spine has been performed only in a minority of the patients and the true incidence of compression fractures cannot be estimated.

The incidence of gastric or peptic ulcer and cataract among our patients was not remarkably high for a group of elderly persons.

Some authors recommend a trial of non-steroidal drugs for uncomplicated polymyalgia rheumatica, because of the risk of corticosteroid side effects (22, 26). A few studies report a high incidence of adverse reactions to corticosteroid therapy (42, 125). Most authors, however, report a relatively low rate of side effects like us (10, 27, 36, 76, 106). When evaluating the morbidity in a group of elderly persons like most patients with GCA, it is important to compare the results with the morbidity in the general population, as we have done in our study. None of the other reports includes such

an analysis of the side effects.

Corticosteroid treatment is the only therapy proved to prevent blindness in GCA (15). We recommend corticosteroid treatment to all patients with GCA, regardless of clinical group. The duration of treatment must be individualised and can only be determined by trial and error. The corticosteroid dosage should be the lowest one that controls the patient's symptoms. The corticosteroid-treatment in GCA may be considered safe both with respect to significant adverse drug reactions and as regards complications of the GCA.

Mortality in GCA (Papers IV and V)

Between 1978 and 1984 nine fatal cases of GCA were observed at the departments of pathology in Göteborg. Two of the victims were not known to have GCA until autopsy. For five of the patients the diagnosis was verified by temporal artery biopsy before death. Two patients had a clinical diagnosis of polymyalgia rheumatica years before death. Temporal artery biopsy had been performed in one of them without showing arteritis.

The causes of death in the series of nine fatal cases were GCA in coronary arteries in two patients, GCA in cerebral arteries in five and GCA causing aortic aneurysms in two cases. The causes of death and microscopical findings are summarised in table IV.

Myocardial infarction

We report two patients with GCA in the coronary arteries. One of them (case 1) suffered from myocardial infarction on the fourth day of treatment and she died after a further week. The other patient had been treated with prednisolone for three years because of polymyalgia reumatica. During a flare-up of the disease, she developed myocardial infarction and progressive cerebral stroke, both due to giant cell arteritis.

In the first case, the short corticosteroid treatment did not prevent the fatal outcome. The second case illustrates that polymyalgia rheumatica is a clinical manifestation of GCA and that severe arteritis in vital arteries can occur during a flare-up of the arteritis.

Microscopic examination of the coronary arteries is not routinely performed at autopsies and the true incidence of GCA in the coronary arteries is thus not known. The prevalence of GCA in cardiological practice is unknown and the disease has been described as a "cardiological blind spot" (54). A few case reports of fatal myocardial infarctions have been published previously (22, 86, 96, 104).

Aortic aneurysm

The risk of sudden death due to GCA in the aorta with rupture of an aneurysm is illustrated by two cases. In one of them (case 3) the diagnosis of GCA was not established until autopsy. Before admission to hospital she had experienced increased fatigue and fever for some months. The other patient had been on corticosteroid treatment for two months when during a flare-up of the disease, she suddenly developed chest pain and died of a dissecting aneurysm of the aorta. The flare-up was only indicated by an elevation of

Table IV **Summary of causes of death and microscopical findings in different arteries in nine fatal cases of GCA**

(0 = not examined; - no inflammation; + slight, ++ moderate; +++ severe inflammation)

Case	Patient Age	Sex	Cause of death	Temporal artery (biopsy)	Coronary artery	Aorta and braches	Cerebral arteries
1	73	F	Myocardial infarction	++	++	++	0
2	85	F	Myocardial infarction	-	+++	+	++
3	85	F	Dissecting aneurysm of the aorta	0	0	+++	0
4	79	F	Dissecting aneurysm of the aorta	+++	+	++	+
5	75	F	Cerebral stroke	+++	+	+	+++
6	69	M	Cerebral stroke	0	0	0	+++
7	76	F	Cerebral stroke	0	0	+	+
8	87	F	Cerebral stroke	+++	0	+	++
9	75	F	Cerebral stroke	+++	-	+	+++

ESR, with no headache or muscular discomfort. The possibility of GCA in the aorta was not realised until the patient suddenly died of a ruptured aneurysm 14 days after admission to hospital.
In the first case, fever and fatigue were the only symptoms until the aneurysm developed. The patient's delay may have contributed to the fatal course. The second case shows that the ESR is a valuable aid to detection of flare-ups of GCA and that aortic aneurysm is an important differential diagnosis in a GCA patient with chest pain.

The first report of aortitis caused by GCA was given in 1937 by Sproul and Hawthorne (132). Further evidence of GCA in the aorta was presented by Gilmour in 1941 (40). Hamrin (45) and Östberg (147) found aortic arch syndrome in 14 out of 93 (15%) patients with GCA. At the Mayo Clinic,

involvement of the aorta or its major branches was found in 34 out of 248 (14%) patients with GCA (73). Three patients with aortitis died of aortic rupture in that series.

Cerebral ischaemia

Death due to cerebral ischaemia in connection with GCA is illustrated by five cases. One woman had been treated with corticosteroids for six years under the diagnosis of polymyalgia rheumatica and suffered hemiparesis during a flare-up of the disease. The flare-up was indicated by muscular pain in her back and upper limbs for about six months. The other patients developed their cerebral ischaemia before corticosteroids were given or after less than two weeks of treatment. In one of the patients the diagnosis was not established until after death. One of the patients had a normal ESR despite an intense arteritis, probably due to a myeloproliferative disorder together with the GCA. These cases draw attention to the possibility of GCA in a patient with signs of cerebral ischaemia and raised acute inflammatory phase reactants.

With the exception of impaired vision, neurological abnormalities caused by GCA are rare (51). Patients with symptoms indicating vertebral artery involvement with brainstem lesions have been described (97). GCA in the cerebral arteries was reviewed in 1972 by Wilkinson and Russel (138). They found eight cases in the literature and reported four deaths resulting from GCA among their own cases. Arteritis was found in the vertebral, ophthalmic and posterior ciliary arteries. The carotids and central retinal arteries were less commonly involved. They observed a sharply defined upper border of the arteritic process about 5 mm above the point of dural perforation. The ophthalmic artery was also involved only outside the dura. Our findings of arteritis of varying severity in intracranial parts of arteries in six patients (case 2 and 4-8) are not in accordance with the opinion that GCA is only an extracranial arteritis. However, in case 9 arteritis was found only extracranially. Chronic arteritis of the intracranial internal carotid arteries was described as early as in 1941 by Gilmour (40). Arteritis in the circle of Willis was reported in 1968 by Kjeldsen and Reske-Nilsen (72). Crompton has reported arteritis in the chiasmatic and pituitary arteries (28).

None of our nine patients with fatal GCA were receiving adequate corticosteroid maintenance treatment. The ischaemic catastrophies started before or during the first weeks of corticosteroid treatment in seven of the patients.

The two patients with polymyalgia rheumatica known for three and six years respectively had elevated ESR and symptoms indicating insufficient control of the arteritic process.

From previous studies, we know that there are about 40 new cases of GCA annually in Göteborg (11). The nine fatal cases were seen during a period of seven years, during which about 280 cases of GCA are estimated to have been diagnosed. Systematic collection of fatal cases was not done and nine fatal cases of 280 may thus be considered a minimum figure.

Long-term mortality in GCA

In the long-term follow-up study of 90 corticosteroid- treated patients with GCA, the expected and observed mortality rates were as shown in table V. After five years, the mortality was lower than expected. This difference is significant ($p < 0.05$). After 10 years, the difference was not statistically significant.

Table V **Observed mortality in a series of orginally 90 patients with GCA (68 women and 22 men) compared with expected mortality based on data from the official Swedish statistics**

Years from diagnosis	Number of deaths					
	Observed			Expected		
	women	men	all	women	men	all
5	8	3	11*	13	7	20
10	22	11	33	13	30	43

* $p < 0.05$ two-sided test with a Poisson distributed test variable

Table VI **Observed and expected numbers of deaths among 42 patients with giant cell arteritis divided into three main groups of diseases.**

Causes of death	Observed			Expected deaths		
	All	men	women	All	men	women
Vascular diseases	25	6	19	26	8	18
Malignant diseases	7	4	3	10	3	7
Infections	7	4	3	4	1	3

In table VI we compare the observed number of deaths from vascular, malignant and infectious diseases with the expected numbers of deaths in the general population of the same age and sex in the same period of time. The mortality rates in the three groups of diseases were not increased in our patients.

Mortality rates among GCA patients similar to those in the general population have been found in studies from the Mayo Clinic, USA (26, 47, 58), Scotland (64), Denmark (17, 77) and France (41, 42). One study, based on patients with GCA treated at the Departments of Ophthalmology and Neurology at a London hospital (43), has shown an increased mortality among women but not among men.

Our conclusion is that, although GCA can be a cause of death through involvement of vital arteries, fatal complications of GCA are so rare in well-treated patients that they do not influence the overall mortality rate.

CONCLUSIONS

- The mononuclear cell infiltration in the arterial wall of GCA patients is mainly compesed of T-helper lymphocytes and macrophages.
- About 15 - 40 % of the infiltrating T lymphocytes express HLA-DR antigen in situ, indicating immunological activation.
- In the blood of GCA patients, on average 6 per cent of the T lymphocytes express HLA-DR antigen before treatment with prednisolone.
- The number of T-helper cells expressing HLA-DR antigen is not altered after 6-10 days of treatment with prednisolone.
- Arterial smooth muscle cells in GCA patients do not express HLA-DR antigen, in contrast to observations in specimens from patients with atherosclerosis.
- In peripheral blood, the proportions of T lymphocytes, T-helper and T-suppressor lymphocytes were within the normal range in untreated GCA patients.
- GCA can be a cause of death by involvement of coronary and cerebral arteries and the aorta.
- Corticosteroid treatment in GCA does not increase the mortality or morbidity but improves quality of life and reduces suffering in GCA patients.
- The median duration of corticosteroid treatment in GCA was five years. A quarter of the surviving patients were still on treatment after nine years.

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to all patients, colleagues, nurses, technicians, secretaries and members of my family who, in so many ways, made this work possible. In particular, I want to thank:

- Dr Bo Eric Malmvall, my supervisor and friend. He introduced me to the study of giant cell arteritis and his never-failing support, continuous encouragement and constructive criticism made it possible to complete it.
- Dr Bengt-Åke Bengtsson for most valuable support and constructive criticism. Together with Dr Malmvall, he initiated the present study and their collection of patients made my long-term follow-up study possible.
- Professor Sten Iwarson, for stimulating discussions and advice.
- My co-workers Drs Roland Jonsson, Göran K Hansson, Andrej Tarkowski, Tommy Söderström, Johan Säve-Söderbergh and Elisabeth Nordborg for numerous discussions, help and collaboration.
- The laboratory technicians Maria Heyden and Marianne Hådén for expert aid in the laboratory work.
- Mrs Yvonne Ballard, Mrs Inger Gyllensten, Mrs Monica Lohm-Muhren and Miss Maria Norberg for excellent secretarial assistance.
- Dr Anders Odén and Mr Nils-Gunnar Persson for help with the statistical analysis.
- Mr John Gulliver for revising the English manuscripts.
- My wife Runa and our children Linnea, Joel and Daniel for all their patience, love and support.
- This study was supported by grants from the Göteborg Medical Society, the Medical Faculty, University of Göteborg, the Swedish Medical Research Council (projects no 7338 and 6816), the Swedish National Association against Rheumatism, Prof. Nanna Svartz Foundatiion and Mrs Torborg Lundqvist.

REFERENCES

1. Alestig K, Barr J. Giant-cell arteritis. A biopsy study of polymyalgia rheumatica, including one case of Takayasu's disease. Lancet 1963; i:1228-30.

2. Armstrong R D, Behn A, Myles A, Panayi G S, Welsh K I. Histocompatibility Antigens in Polymyalgia Rheumatica and Giant Cell Arteritis. J Rheumatol 1983; 10:(4):659-61.

3. Ayoub W T, Franklin C M, Torretti D. Polymyalgia Rheumatica. Duration of Therapy and Long-Term Outcome. Am J Med 1985; 79:309-15.

4. Bach F H. The HLA class II genes and products: the HLA-D region. Immunol Today 1985; 6:89-94.

5. Bacon P A, Doherty S M, Zuckerman A J. Hepatitis-B antibody in polymyalgia rheumatica. Lancet 1975; ii:476-8.

6. Banks P M, Cohen M D, Ginsburg W W, Hunder G G. Immunohistologic and cytochemical studies of temporal arteritis. Arthritis Rheum 1983; 26:1201-7.

7. Barrier J, Bignon J-D, Soulillou J-P, Grolleau J. Increased prevalence of HLA-DR4 in giant-cell arteritis. N Engl J Med 1981; 305:104-5.

8. Beeson P B, Mc Dermott W. Textbook of medicine. W B Saunders Company, Philadelphia, 14th edition 1975; 1:175.

9. Beevers D G, Harpur J E, Turk K A D. Giant cell arteritis - the need for prolonged treatment. J Chron Dis 1973; 26:571-84.

10. Behn A R, Perera T, Myles A B. Polymyalgia rheumatica and corticosteroids: how much for how long? Ann Rheum Dis 1983; 42:374-8.

11. Bengtsson B-Å, Malmvall B-E. The epidemiology of giant cell arteritis including temporal arteritis and polymyalgia rheumatica. Arthr Rheum 1981; 24(7):899-904.

12. Bengtsson B-Å, Malmvall B-E. Prognosis of giant cell arteritis including temporal arteritis and polymyalgia rheumatica. A follow-up study on ninety patients treated with corticosteroids. Acta Med Scand 1981; 209:337-45.

13. Bengtsson B-Å, Malmvall B-E. Giant cell arteritis. Acta Med Scand 1982; Suppl. 658.

14. Benlahrache C, Segond P, Auquier L, Bouvet J-P. Decrease of the OKT8 positive T cell subset in polymyalgia rheumatica. Lack of correlation with disease activity. Arthritis Rheum 1983; 26(12):1472-80.

15. Birkhead N C, Wagener H P, Shick R M. Treatment of temporal arteritis with adrenal corticosteroids. Results in fifty-five cases in which lesion was proved at biopsy. JAMA 1957; 163(10):821-6.

16. Bloch T, Waller B F, Vakili S T. Giant Cell Arteritis of the Coronary Arteries. Indiana Med 1987; 80(3):262-4.

17. Boesen P, Freiesleben Sørensen S. Giant cell arteritis, temporal arteritis, and polymyalgia rheumatica in a danish county. A prospective investigation, 1982 - 1985. Arthritis Rheum 1987; 30(3):294-9.

18. Brickell P M, Richardson N E, Mc Connell I, Feinstein A. Distinct populations of class II molecules identified by monoclonal antibodies. Clin exp Immunol 1983; 54:117-26.

19. Bridgeford P H, Lowenstein M, Bocanegra T S, Vasey F B, Germain B F, Espinoza L R. Polymyalgia rheumatica and giant cell arteritis: histocompatibility typing and hepatitis-B infection studies. Arthritis Rheum 1980; 23(4):516-8.

20. Burmester GR, Jahn B, Gramatzki M, Zacker J, Kalden JR. Activated T cells in vivo and in vitro: divergence in expression of Tac and Ia antigens in the nonblastoid small T cells of inflammation and normal T cells activated in vitro. J Immunol 1984;133(3):1230-4.

21. Ceuppens J L, Goodwin J S, Searles R P. The Presence of Ia Antigen on Human Peripheral Blood T Cells and T-cell Subsets: Analysis with Monoclonal Antibodies and the Fluorescence-Activated Cell Sorter. Cell Immunol 1981; 64:277-92.

22. Chang R W, Fineberg H V. Risk-Benefit Considerations in the Management of Polymyalgia Rheumatic. Med Decis Making 1983; 3(4):459-75.

23. Chelazzi G, Broggini M. Abrnomalities of peripheral blood T lymphocyte subsets in polymyalgia rheumatica. Clin Exp Rheumatol 1984; 2:333-6.

24. Chemnitz J, Christensen B C, Chrisoffersen P, Garbarsch C, Hansen T M, Lorenzen I. Giant cell arteritis. Histological, immunohistochemical and electronmicroscopic studies. Acta Path Microbiol Immunol Scand Sect A 1987; 95:251-62.

25. Chess J, Albert D M, Bhan A K, Paluck E I, Robinson N, Collins B, Kaynor B. Serologic and immunopathologic findings in temporal arteritis. Am J Ophtalmol 1983; 96:283-9.

26. Chuang T-Y, Hunder G G, Ilstrup D M, Kurland L T. Polymyalgia Rheumatica. A 10-year epidemiologic and clinic study. Ann Intern Med 1982; 97:672-80.

27. Coomes E N, Ellis R M, Kay A G. A prospective study of 102 patients with the polymyalgia rheumatica syndrome. Rheuma Rehab 1976; 15:270-6.

28. Crompton M R. The visual changes in temporal (giant-cell) arteritis. Report of a case with autopsy findings. Brain 1959; 82:377-90.

29. Dimitriu-Bona A, Burmester G R, Waters S J, Winchester R J. Human mononuclear phagocyte differentiation antigens. I. Patterns of antigenic expression on the surface of human monocytes and macrophages defined by monoclonal antibodies. J Immunol 1983; 130(1):145-52.

30. Elling H, Skinhøj P, Elling P. Hepatitis B Virus and polymyalgia rheumatica: a search for HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb. Ann Rheum Dis 1980; 39:511-3.

31. Elling H, Elling P. Decreased Level of Suppressor/Cytotoxic T Cells (OKT8+) in Polymyalgia Rheumatica and Temporal Arteritis: Relation to Disease Activity. J Rheumatol 1985; 12(2): 306-9.

32. Enzmann D, Scott W R. Intracranial involvement of giant-cell arteritis. Neurology 1977; 27:794-7.

33. Espinoza L R, Bridgeford P, Lowenstein M, Bocanegra T S, Vasey F B, Germain B F. Polymyalgia Rheumatica and Giant Cell Arteritis: Circulating Immune Complexes. J Rheumatol 1982; 9(4): 556-60.

34. Fauchald P, Rygvold O, Øystese B. Temporal Arteritis and Polymyalgia Rheumatica. Clinical and biopsy findings. Ann Intern Med 1972; 77:845-52.

35. Fauci A S, Dale D C. The effect of in vivo hydrocortisone on subpopulations of human lymphocytes. J Clin Invest 1974; 53:240-6.

36. Fernandez-Herlihy L. Duration of Corticosteroid Therapy in Giant Cell Arteritis. J Rheumatol 1980; 7(3):361-4.

37. Fessel W J. Polymyalgia rheumatica, temporal arteritis, and contact with birds. Lancet 1969; ii:1249-50.

38. Fye K H, Zulman J I. Giant cell arteritis diagnosed by carotid endarterectomy. J Rheumatol 1985; 12(3): 625-7.

39. Gallagher P, Jones K. Immunohistochemical findings in cranial arteritis. Arthritis Rheum 1982; 25(1):75-9.

40. Gilmour J R. Giant-cell chronic arteritis. J Pathol 1941; 53:263-77.

41. Godeau P, Aubert L, Guillevin L, Tard P, Maaouni A, Wechsler B, Bletry O, Herreman G. Aspect clinique évolution et pronostic de la maladie de Horton. Étude rétrospective de 47 observations. Ann Med Interne 1982; 133(6):393-400.

42. Gouet D, Marechaud R, Alcalay M, Becq-Giraudon B, Bontoux D, Lefevre J-P, Gil R, Risse J-F, Sudre Y. Survival in giant cell arteritis: A 14-year survey of 87 patients. J Rheumatol 1985; 12(6):1209-10.

43. Graham E, Holland A, Avery A, Russell R W R. Prognosis in giant-cell arteritis. Brit Med J 1981; 282:269-71.

44. Hamrin B, Jonsson N, Landberg T. Arteritis in "polymyalgia rheumatica". Lancet 1964; i:397-401.

45. Hamrin B. Polymyalgia arteritica. Acta Med Scand 1972; 192:suppl 533.

46. Hansson G K, Jonasson L, Holm J, Claesson-Welsh L. Class II MHC antigen expression in the atherosclerotic plaque: smooth muscle cells express HLA-DR, HLA-DQ and the invariant gamma chain. Clin exp Immunol 1986; 64:261-8.

47. Hauser W A, Ferguson R H, Holley K E, Kurland L T. Temporal arteritis in Rochester, Minnesota, 1951 to 1967. Mayo Clin Proc 1971; 46:597-602.

48. Haynes B F, Fauci A S. The Differential Effect of In Vivo Hydrocortisone on the Kinetics of Subpopulations of Human Peripheral Blood Thymus-Derived Lymphocytes. J Clin Invest 1978; 61:703-7.

49. Hazleman B L, Maclennan I C M, Esiri M M. Lymphocyte proliferation to artery antigen as a positive diagnostic test in polymyalgia rheumatica. Ann Rheum Dis 1975; 34:122-7.

50. Healey L A. Long-Term Follow-Up of Polymyalgia Rheumatica: Evidence for Synovitis. Arthritis Rheum 1984; 13(4):322-8.

51. Hollenhorst R W, Brown J R, Wagener H P, Shick R M. Neurologic aspects of temporal arteritis. Neurology 1960; 10:490-8.

52. Horton B T, Magath T B, Brown G E. An undescribed form of arteritis of the temporal vessels. Proceedings of the staff meetings of the Mayo Clinic 1932; 7:700-1.

53. Horton B T, Magath T B. Arteritis of the temporal vessels: Report of even cases. Staff meetings of the Mayo Clinic 1937; 548-53.

54. How J, Strachan R W, Bewsher P D. Giant cell arteritis - a cardiological blind spot? Am Heart J 1980; 100 (3):405-7.

55. Hsu S-M, Raine L, Fanger H. Use of Avidin-Biotin-Peroxidase complex (ABC) in immunoperoxidase techniques: A comparison between ABC and unlabeled antibody (PAP) procedures. J Histochem Cytochem 1981; 29(4):577-80.

56. Hsu S-M, Jaffe E S. Phenotypic Expression of T Lymphocytes in Thymus and Peripheral Lymphoid Tissues. Am J Pathol 1985; 121:69-78.

57. Hunder G G. More on Polymyalgia Rheumatica and Giant Cell Arteritis. West J Med 1984; 141:68-70.

58. Huston K A, Hunder G G. Temporal Arteritis. A 25-Year Epidemiologic, Clinical, and Pathologic Study. Ann Intern Med 1978; 88:162-7.

59. Hutchinson J. Diseases of the arteries. Arch Surg (London) 1890; 1:323.

60. Hämmerling G J. Tissue Distribution of Ia Antigens and their Expression on Lymphocyte Subpopulations. Transplant Rev 1976; 30:64-82.

61. Iwatani Y, Amino N, Mori H, Asari S, Ina K, Ennyu K, Miyai K. Effects of various isolation methods for human peripheral lymphocytes on T cell subsets determined in a Fluorescence Activated Cell Sorter (FACS), and demonstration of a sex difference of suppressor/cytotoxic T cells. J Immunol Methods 1982; 54:31-42.

62. Jansson R, Karlsson A, Forsum U. Intrathyroidal HLA-DR expression and T lymphocyte phenotypes in Graves' thyrotoxicosis, Hashimoto's thyroiditis and nodular colloid goitre. Clin exp Immunol 1984; 58:264-72.

63. Jipp P, Fehring K. Polymyalgia rheumatica und Riesenzellarteriitis. DMW 1984; 109(43), 1635-8.

64. Jonasson F, Cullen J F, Elton R A. Temporal arteritis. A 14-year epidemiological, clinical and prognostic study. Scot med J 1979; 24:111-7.

65. Jonasson L, Holm J, Skalli O, Gabbiani G, Hansson G K. Expression of Class II Transplantation Antigen on Vascular Smooth Muscle Cells in Human Atherosclerosis. J Clin Invest 1985; 76:125-31.

66. Jones J G, Hazleman B L. Prognosis and management of polymyalgia rheumatica. Ann Rheum Dis 1981; 40:1-5.

67. Jonsson R, Klareskog L, Bäckman K, Tarkowski A. Expression of HLA-D-Locus (DP, DQ, DR) - coded antigens, 2-microglobulin, and the interleukin-2 receptor in Sjögren's syndrome. Clin Immunol Immunopathol 1987;45:235-43.

68. Kalbfleich J D, Prentice R L. The statistical analysis of failure. Time Data, Wiley, New York 1980.

69. Kasai M, Iwamori M, Nagai Y, Okumura K, Tada T. A glycolipid on the surface of mouse natural killer cells. Eur J Immunol 1980;10:175-80.

70. Kay R H, Pooley R, Herman M V. Unsuspected Giant Cell Arteritis Diagnosed at Open Heart Surgery. Arch Intern Med 1982; 142:1378-9.

71. Kimmelstiel P, Gilmour M T, Hodges H H. Degeneration of elastic fivers in granulaomatous giant cell arteritis (temporal arteritis). Arch Pathol 1952; 54:157-68.

72. Kjeldsen M H, Reske-Nielsen E. Pathological changes of the central nervous system in giant-cell arteritis. Acta Ophtalmol 1968; 46:49-56.

73. Klein R G, Hunder G G, Stanson A W, Sheps S G. Large Artery Involvement in Giant Cell (Temporal) Arteritis. Ann Intern Med 1975; 83:806-12.

74. Klinkhoff A V, Reid G D, Moscovich M. Aortic regurgitation in giant cell arteritis. Arthritis Rheum 1985; 28(5):582-5.

75. von Knorring J, Somer T. Malignancy

76. von Knorring J. Treatment and Prognosis in Polymyalgia Rheumatica and Temporal Arteritis.A ten-year survey of 53 patients. Acta Med Scand 1979; 205:429-35.

77. Knudsen L, Christensen G, Krohn L. Polymyalgia rheumatica syndrome. Scand J Rheumatol 1982; 11:17-20.

78. Kogstad O A. Polymyalgia Rheumatica and its Relation to Arteritis Temporalis. Acta Med Scand 1965; 178:591-8.

79. Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 1975; 256:495-7.

80. Larson DM, Fujiwara K, Alexander RW, Gimbrone MA. Heterogenicity of myosin antigenic expression in vascular smooth muscle in vivo. Lab Invest 1984;50(4):401-7.

81. Ledbetter J A, Evans R L, Lipinski M, Cunningham-Rundles C, Good R A, Herzenberg L A. Evolutionary conservation of surface molecules that distinguish T lymphocyte helper/inducer and cytotoxic/suppressor subpopulations in mouse and man. J Exp Med 1981; 153:310-23.

82. Leonard W J, Depper J M, Uchiyama T, Smith K A, Waldman T A, Greene W C. A monoclonal antibody that appears to recognize the receptor for human T-cell growth factor; partial characterization of the receptor. Nature 1982; 300:267-9.

83. Lernfelt B, Landahl S, Svanborg A. Coronary heart disease at 70, 75 and 79 years of age. A longitudinal study with special reference to sex difference and mortality. Submitted 1987.

84. Liang G C, Simkin P A, Mannik M. Immunoglobulins in Temporal Arteries. An immunofluorescent study. Ann Intern Med 1974; 81:19-24.

85. Liang M, Greenberg H, Pincus T, Robinson W S. Hepatitis-B antibody in polymyalgia rheumatica. Lancet 1976; i:43.

86. Lie J T, Failoni D D, Davis jr, D C. Temporal Arteritis With Giant Cell Aortitis, Coronary Arteritis, and Myocardial Infarction. Arch Pathol Lab Med 1986; 110:857-60.

87. Life tables for the decade 1971-1980. Official statistics of Sweden, Stockholm 1984.

88. Lindahl G, Hedfors E, Klareskog L, Forsum U. Epithelial HLA-DR expression and T lymphocyte subsets in salivary glands in Sjögren's syndrome. Clin exp Immunol 1985; 61:475-82.

89. Lindblad S, Klareskog L, Hedfors E, Forsum U, Sundström C. Phenotypic characterization of synovial tissue cells in situ in different types of synovitis. Arthritis Rheum 1983; 26(11):1321-32.

90. Lindblad S, Hedfors E. Arthroscopic and immunohistologic characterization of knee joint synovitis in osteoarthritis. Arthritis Rheum 1987;30(10):1081-8.

91. Lipton R B, Rosenbaum D, Mehler M F. Giant cell arteritis causes recurrent posterior circulation transient ischemic attacks with respond to corticosteroid. Eur Neurol 1987; 27:97-100.

92 . Lowenstein M B, Bridgeford P H, Vasey F B, Germain B F, Espinoza L R. Increased frequency of HLA-DR3 and DR4 in polymyalgia rheumatica-giant cell arteritis. Arthritis Rheum 1983; 26(7):925-7.

93 . Malmvall B-E, Bengtsson B-Å, Nilsson L-Å, Bjursten L-M. Immune complexes, rheumatoid factors, and cellular immunological parameters in patient with giant cell arteritis. Ann Rheum Dis 1981; 40:276-80.

94. Mann D L, Sharrow S O. HLA-DRw alloantigens can be detected on peripheral blood T lymphocytes. J Immunol 1980; 125(5):1889-96.

95. Marchionni N, Di Bari M, Ferrucci L, Moschi G, Dabizzi RP, Di Donato M, Biancalani M, Gori F. Giant-cell arteritis causing severe aortic regurgitation secondary to aneurysm of the ascending aorta - A case report. Angiology 1987; 38(9):712-6.

96. Martin J F, Kittas C, Triger D R. Giant cell arteritis of coronary arteries causing myocardial infarction. Br Heart J 1980; 43:487-9.

97. Meadows S P. Temporal or Giant Cell Arteritis. Proceedings of the Royal Society of Medicine. 1966; 59:329-33.

98. Meeker T C, Miller RA, Link MP, Bindl J, Warnke R, Levy R. A unique human B lymphocyte antigen defined by a monoclonal antibody. Hybridoma 1984; 3:305-20.

99. Melton L J, Bickerstaff L K, Hollier L H, van Peenen H J, Lie J T, Pairolero P C, Cherry K J, O'Fallon W M. Changing incidence of abdominal aortic aneurysms: A population-based study. Am J Epidemiol 1984; 120(3):379-86.

100. Molldrem N D, Olin R. Polymyalgia Rheumatica with Temporal and Coronary Arteritis. A case report. Minn Med 1972; 55:19-23.

101. Monteiro M L R, Coppeto J R, Greco P. Giant Cell Arteritis of the Posterior Cerebral Circulation Presenting With Ataxia and Ophtalmoplegia. Arch Oprhtalmol 1984; 102:407-9.

102. Morimoto C, Letvin N L, Distaso J A, Aldrich W R, Schlossman S F. The isolation and characterization of the human suppressor inducer T cell subset. J Immunol 1985; 134(3):1508-15.

103. Morimoto C, Letvin N L, Boyd A W, Hagan M, Brown H M, Kornacki M M, Schlossman S F. The isolation and characterization of the human helper inducer T cell subset. J Immunol 1985; 134(6):3762-9.

104. Morrison A N, Abitbol M. Granulomatous arteritis with myocardial infarction: A case report with autopsy findings. Ann Intern Med 1955; 42: 691-700.

105. Moyer C F, Reinisch C L. The role of vascular smooth muscle cells in the experimental autoimmune vasculitis. I. The initiation of delayed type hypersensitivity angiitis. Am J Pathol 1984; 117:380-90.

106. Myles A B. Polymyalgia rheumatica and giant cell arteritis: A seven-year survey. Rheumatol Rehab 1975; 14:231-5.

107. Nilsson M H. Trochanteric fractures. Treatment by Ender intermedullary fixation. Observed and predicted incidence in the Stockholm area. Stockholm 1984; Dissertation.

108. O'Brien J P. A concept of diffuse actinic arteritis. The role of actinic damage to elastin in "age change" and arteritis of the temporal artery and in polymyalgia rheumatica. Br J Dermatol 1978; 98:1-13.

109. Ojeda V J, Paton R, Smith K H, Panegyres P K. Aortic aneurysm, giant-cell aortitis and polymyalgia rheumatica: report of a surgical case. Aust N Z J Surg 1983; 53:375-8.

110. Olsson T, Henriksson K G, Klareskog L, Forsum U. HLA-DR expression, T lymphocyte phenotypes, OKM1 and OKT9 reactive cells in inflammatory myopathy. Muscle Nerve 1985; 8:419-25.

111. Ornilla E, Swannell AJ, Dixon A StJ. Myalgia and birdkeeping. Lancet 1970;ii:96.

112. Osnes M, Lassen J. Artritter og polymyalgier ved yersinia enterocolitica infeksjoner. T norske Laegeforen 1974; 94:225-8.

113. Palacios R. Mechanism of T Cell Activation: Role and Functional Relationship of HLA-DR Antigens and Interleukins. Immunol Rev 1982; 63:73-110.

114. Papaioannou C C, Hunder G G, McDuffie F C. Cellular immunity in polymyalgia rheumatica and giant cell arteritis. Lack of response to muscle or artery homogenates. Arthritis Rheum 1979; 22(7):740-5.

115. Papaioannou C C, Gupta R C, Hunder G G, McDuffie F C. Circulating immune complexes in giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum 1980; 23(9):1021-5.

116. Papajiannis S P, Spina M, Gotte L. Sequential Degradation and Phagocytosis of Heterologous Elastin. Arch Path 1970; 89:434-9.

117. Park J R, Hazleman B L. Immunological and histological study of temporal arteries. Ann Rheum Dis 1978; 37:238-43.

118. Park J R, Jones J G, Harkiss G D, Hazleman B L. Circulating immune complexes in polymyalgia rheumatica and giant cell arteritis. Ann Rheum Dis 1981; 40:360-5.

119. Parker F, Healey L A, Wilske K R, Odland G F. Light and electronmicroscopic studies on human temporal arteritis with special reference to alternations related to senescence, atherosclerosis and giant cell arteritis. Am J Pathol 1975; 79:57-80.

120. Paulley J W. Anarthritic rheumatoid disease. Lancet 1956; ii:946.

121. Paulley J W. Coronary Ischaemia and Occlusion in Giant Cell (Temporal) Arteritis. Acta Med Scand 1980; 208:257-63.

122. Porsman V A. Proc II. Congr Europ Rheum (editorial scientia, Barcelona) 1951: 479.

123. Radda T M, Ulrich W, Menzel E J. Elektronenmikroskopische und immunhistologische Untersuchungen bei Patienten mit Arteriitis temporalis Horton. Wiener Medizinische Wochenschrift 1984; 134; suppl 81:1-24.

124. Rasmussen L H, Garbarsch C, Lorenzen I. Injury and repair of smaller muscular and elastic arteries. A light microscopic study on the different healing patterns of rabbit femoral and carotid arteries following dilatation injuries by a balloon catheter. Virchows Arch A 1987; 411:87-92.

125. Rubinow A, Brandt K D, Cohen A S, Sack B. Iatrogenic Morbidity Accompanying Suppression of Temporal Arteritis by Adrenal Corticosteroids. Ann Opthalmol 1984; 16(3): 258-65.

126. Salisbury R S, Hazleman B L. Successful treatment of dissecting aortic aneurysm due to giant cell arteritis. Ann Rheum Dis 1981; 40:507-8.

127. Sauerbruch T, Stuhlinger B, Kaess H. Immunhistologische Untersuchungen bei einem Fall von Riesenzellarteritis (Arteritis temporalis). DMW 1973; 98:283-4.

128. Segerberg-Konttinen M, Bergroth V, Jungell P, Malmström M, Nordström D, Sane J, Immonen I, Konttinen Y T. T lymphocyte activation state in the minor salivary glands of patients with Sjögren's syndrome. Ann Rheum Dis 1987; 46:649-53.

129. Shick RM, Baggenstoss AH, Fuller BF, Polley HF. Effects of cortisone and ACTH on periarteritis nodosa and cranial arteritis. Staff meetings of the Mayo Clinic 1950:492-4.

130. Soelberg Sørensen P, Lorenzen I. Giant-Cell Arteritis, Temporal Arteritis and Polymyalgia Rheumatica. Acta Med Scand 1977; 201:207-13.

131. Spence R K, Estella F, Gisser S, Schiffman R, Camishion R C. Thoracic aortic aneurysm secondary to giant cell arteritis: A reappraisal of etiology, treatment and possible prevention. J Cardiovasc Surg 1985; 26:492-5.

132. Sproul E E, Hawthorne J J. Chronic diffuse mesaortitis. Report of two cases of unusual type. Amer J Path 1937; 13:311-23.

133. Statistisk årsbok 1984. Statistical abstract of Sweden 1984. Official statistics of Sweden. National Bureau of statistics. Stockholm 1984;vol 70.

134. Sutherland R, Delia D, Schneider C, Newman R, Kemshead J, Greaves M. Ubiquitous cell-surface glycoprotein on tumor cells is proliferation-associated receptor for transferrin. Proc Natl Acad Sci USA 1981; 78(7):4515-9.

135. Waaler E, Tönder O, Milde E-J. Immunological and histological studies of temporal arteries from patients with temporal arteritis and/or polymyalgia rheumatica. Acta Pathol Microbiol Scand Sect A 1976; 84:55-63.

136. Velvart M, Felder M, Fehr K, Sommermeyer G, Cancer M, Wagenhäuser F J, Böni A. Temporal arteritis in polymyalgia rheumatica: Immune complex deposits and the role of the leukocyte elastase in the pathogenesis. Z Rheumatol 1983; 42:320-7.

137. White A G, Innes E H. Polymyalgia rheumatica and contact with melopsittacus undulatus. Rheum Phys Med 1972; 11:380-4.

138. Wilkinson I M S, Russell R W R. Arteries of the Head and Neck in Giant Cell Arteritis. A pathological study to show the pattern of arterial involvement. Arch Neurol 1972; 27:378-91.

139. Williams R C, Webster A D B, Morito T, Greaves M F. T lymphocyte subpopulations and Ia-positive T cells in patients with immunodeficiency. Clin Exp Immunol 1980; 42:355-63.

140. Wilske K R, Healey L A. Polymyalgia Rheumatica. A Manifestation of Systemic Giant-cell Arteritis. Ann Intern Med 1967; 66:77-86.

141. Vincent F M, Vincent T. Bilateral Carotid Siphon Involvement in Giant Cell Arteritis. Neurosurgery 1986; 18(6):773-6.

142. Wood G S, Warner N L, Warnke R A. Anti-Leu-3/T4 antibodies react with cells of monocyte/macrophage and Langerhans lineage. J Immunol 1983; 131(1):212-6.

143. Youinou P Y, Pennec Y, Tande D, Le Menn G. Immune complexes and autoantibodies in patients with giant cell arteritis and their relationship with autologous rosette-forming cell. Clin Exp Rheumatol 1985; 3:17-21.

144. Yu D T Y, Clements P J, Paulus H E, Peter J B, Levy J, Barnett E V. Human lymphocyte subpopulations. Effect of corticosteroids. J Clin Invest 1974; 53:565-71.

145. Yu D T Y, Mc Cune J M, Fu S M, Winchester R J, Kunkel H G. Two types of Ia positive T cells. Synthesis and exchange of Ia antigens. J Exp Med 1980; 152:89-98.

146. Zilko P, Currey H L F, Vernon-Roberts B. Polymyalgia rheumatica (PMR) and giant cell arteritis: lack of response of peripheral blood lymphocytes to arterial wall homogenate. Ann Rheum Dis 1977; 36:286-7.

147. Östberg G. On arteritis with special reference to polymyalgia arteritica. Acta Pathol Microbiol Scand Sect A 1973; suppl 237:1-59.

GÖTEBORGS UNIVERSITET
GÖTEBORGS UNIVERSITETSBIBLIOTEK

VASASTADENS BOKBINDERI AB
GÖTEBORG 1988