SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2018; 35; Suppl 1: 9-79

Clinical research on sarcoidosis in Finland

Early clinical reports

Kuhlefelt E. Ett fall av febris uveoparotidea subchronica (Heerfordt), (A case of subchronic uveoparotid inflammation, Heerfordt), Finska Läk-Sällsk Handl 1916; 58:867-870 (in Swedish) (1). The manuscript was translated to English and published with the English title in **Br J Ophthalmol 1917; 1:621-623.** Kuhlefelt described a disease in a 21-year old woman who suffered from joint pain, bilaterally enlarged parotic glands and right-sided uveitis. Kuhlefelt mentioned that a similar type disease had been described by Heerfordt. He regarded the disease as a type of tuberculosis. It was not until 1936-37 the uveoparotid fever was classified as a type of sarcoidosis.

Cedercreutz A. "Krankenvorstellungen" (Case reports) Förhandlingar vid Nordisk Dermatologisk Förenings **10:de** möte I Helsingfors, Mercator, 1939: 701" (2)**.** Cedercreutz was a dermatologist and reported the histories of four cases of Boeck's sarcoid at the Nordic Dermatolgy congress in Helsinki in 1938. All four patients had skin lesions on the face and two of them had changes in the hilar regions in chest radiographs.

Clinical Research 1943-2017

The first scientific publications in Finland related to sarcoidosis were written by a dermatologist, Tauno Putkonen, and delt with the Kveim test. He published a series of publications starting with his academic thesis:

Putkonen T. Über die Intrakutanreaktion von Kveim (KvR) bei Lymphogranulomatosis benigna und über das Bild dieser Krankheit in Lichts der Reaktionsergebnisse. (About the intracutaneous Kveim reaction in lymphogranulomatosis benigna and the clinical picture in light of the reaction features). Acta derm-venereol (Sthlm) 1943;23, suppl 10:1-194 (in German) (3).

Putkonen T. Über die Kveimreaktion by Lymphogranulomatoisis benigna. Mit einem Beitrag zur Thermostabilität und Haltbarkeit des Antigens. (About the Kveim reaction in lymphogranulomatosis benigna. With contribution to the termostability and validity of the antigen). Acta derm-venereol (Sthlm) 1945; 25:393-410 (in German) (4).

Putkonen T. Lymfogranulomatosis benigna ja Kveimin reaktio (Lymphogranulomatosis benigna and the Kveim reaction). Duodecim 1945; 61:223-243 (in Finnish) (5).

Putkonen T. A case of skin tuberculosis with a positive Kveim's reaction as late as five years after injection of antigen. Acta Derm Venereol Suppl (Stockh). 1952;32(29):294-296 (6).

Putkonen T. The Kveim reaction. Acta tuberc scand 1959; 38, suppl 45:24-31 (7).
Putkonen prepared Kveim material from lymph nodes and noticed that material from a patients who reacted weakly themselves or not at all to Kveim material was more potent than material from patients who reacted strongly and rapidly to the intradermally injected material. Due to the limited amount of test material from each source it was difficult to standardize the test. Despite a lot of research the active principle in Kveim material has remained unknown and the test is no longer in clinical use.

In the 1950'ies not much happened around sarcoidosis in Finland. The internists Kuhlbäck and Nyberg reported on hypercalcaemia and renal failure and Aho et al published a paper about spontaneous pneumothorax in three patients with pulmonary sarcoidosis:

Kuhlbäck B, Nyberg W. Hyperkalcemi och njurskada vid sarkoidos (Hypercalcaemia and renal failure in sarcoidosis). Finska Läk-Sällsk Handl 1955; 98:181-185 (in Swedish) (8).

Aho A, Heinivaara O, Mahonen H. Boeck's sarcoid as a cause of spontaneous pneumothorax. Ann Med Intern Fenn 1958; 47:163-167 (9).

These papers will be discussed in more detail below.

As mentioned before the real start of sarcoidosis research in Finland goes back to the 1963 international congress on sarcoidosis in Stockholm (10).

Academic dissertations

A total of 14 academic dissertations dealing with sarcoidosis have been defended at universities in Finland:

1943 Tauno Putkonen. Über die Intrakutanreaktion von Kveim (KvR) bei Lymphogranulomatosis benigna und über das Bild dieser Krankheit in Lichts der Reaktionsergebnisse. (About the intracutaneous Kveim reaction in lymphogranulomatosis benigna and the clinical picture in light of the reaction features) (3).

1968 Kari Määttä. Histological study of mediastinal lymph nodes in clinical sarcoidosis. A report of 86 cases, Turku University (11).

1969 Olof Selroos. The frequency, clinical picture and prognosis of pulmonary sarcoidosis in Finland, Helsinki University (12).

1971 Matti Hannuksela. Erythema nodosum with special reference to sarcoidosis. A clinical study of 343 Finnish adult patients, Helsinki University (13).

1973 Maija Horsmanheimo. Lymphocyte transformation in sarcoidosis, Helsinki University (14).

1975 Pentti Tukiainen. Needle biopsy in diffuse lung manifestations. An analysis of 145 consecutive cases, Helsinki University (15).

1979 Anni Karma. Ophthalmic changes in sarcoidosis, Oulu University (16).

1980 Carola Grönhagen-Riska. Angiotensin converting enzyme and sarcoidosis, Helsinki University (17)**.**

1983 Juhani Elo. Sarkoidoosi. Kliininen tutkimus Varsinais-Suomen tuberkuloosipiirissä vuosilta 1965-1977 (Sarcoidosis. A clinical study in the tuberculosis district of South-Western Finland in 1965-1977), Turku University (in Finnish) (18).

1985 Elli Koivunen. Hematologiset löydökset sarkoidoosissa (Haematological findings in sarcoidosis), Tampere University (in Finnish) (19).

1986 Virpi Oksanen. Neurosarcoidosis. A clinical, laboratory and neuroradiological study, Helsinki University (20).

2000 Anne Pietinalho. Sarcoidosis in Finland and Hokkaido, Japan. A study of two genetically different populations, Helsinki University (21).

2014 Annika Wennerström. The extended MCH haplotypes and their role in sarcoidosis, Helsinki University (22).

2015 Riina Kandolin. Cardiac sarcoidosis and giant cell myocarditis in Finland. Helsinki University (23).

Epidemiology

Riska N, Selroos O. Clinically diagnosed sarcoidosis in Finland in 1960. Acta tuberc pneum scand 1964;44:267-275 (24). Riska and Selroos collected data on all patients who had been hospitalized because of sarcoidosis in Finland in the year 1960. A total of 71 cases with definite or probable diagnosis

of sarcoidosis were found among a population of 4.8 million giving a prevalence of 1.59/10^5. It is obvious that sarcoidosis at this time was a less well known diseases in Finland and probably often misdiagnosed as tuberculosis.

Pätiälä J, Riska N, Selroos O. Sarcoidosis in Finland. Acta med scand 1964; 176, suppl 425:110 (25). In 1960-1961 a total of 1 450 000 mass chest radiographic surveys were performed in Finland. Based on the radiographs the prevalence of sarcoidosis was estimated to be 4.6/100 000 pictures. In 60% of the cases the diagnosis had been confirmed by tissue biopsies. In the same report the prevalence of diagnosed cases in a district of southern Finland – the tuberculosis district of Raseborg – was 5.1/10^5 inhabitants.

Selroos O. Frequency and nature of sarcoidosis in southern Finland. In: La Sarcoïdose, (eds. J Turiaf & J Chabot), Masson et Cie, Paris ,1967 pp 369-372 (26). In a further mass radiographic survey in the Raseborg district in 1959-1965 the prevalence of sarcoidosis was estimated to a mean of 8.1/10^5. In the same period the annual incidence of new cases increased gradually from 2.0/10^5 inhabitants above the age of 15 years in 1959 to 16.1/10^5 in 1965. There were twice as many women as men. Erythema nodosum was 10 times more common in female patients.

As part of his academic thesis Selroos estimated the frequency of sarcoidosis in entire Finland (12). In the 1960's Finland was divided into tuberculosis districts and these were further divided into 46 smaller administrative areas – tuberculosis dispensary areas. In these 46 areas the actual situation of tuberculosis was determined by calculating the number of new tb-positive cases, the number of patients with pulmonary tuberculosis listed in the registry, the number of chronic cases, and the number of fatal cases. Based on these numbers a ranking list was established from the area with the most severe to the mildest tuberculosis situation. The list was divided into four parts with 13 tuberculosis dispensary areas in each. Then by lottery three areas from each of the four parts were selected for detailed investigation of sarcoidosis during the period 1962-1967. A prevalence of 7.5/10^5 was found and an annual incidence of new cases of 5.3/10^5. A great variation in frequency figures were seen between the areas in the study. No statistically significant correlation was noticed between tuberculosis and sarcoidosis. There were more female than male patients (2:1). Most female patients were seen in the 40-49 year age group and most males in the 30-39 year age group.

Elo studied sarcoidosis in the Southwestern part of Finland (18). In this district the mean annual incidence of sarcoidosis in 1974-1977 was 17.6/10^5 inhabitants. The prevalence based on mass chest radiographic examinations in 1971-1980 was 102/10^5.

Poukkala A, Huhti E, Lilja M, Saloheimo M. Incidence and clinical picture of sarcoidosis in a circumscribed geographical area. Br J Dis Chest 1986; 80:138-147 (27). A few years later (1970-1981) the mean annual incidence of sarcoidosis in northern Finland was 14.2/10^5.

Selroos O, Pietinalho A, Löfroos A-B, Hellström P-E, Riska H. Sarcoidosis in Southern Finland 1981-1985. Sarcoidosis 1992; 9, suppl 1: 125-128 (28)**.** Sarcoidosis was diagnosed in 193 patients, 86 women and 61 men; 147 (76%) were biopsy proven. Patients without biopsy support were mostly women with Löfgren's syndrome where biopsy support is normally not necessary. Thirty-one % of the patients belonged to the age group 30-39 years where also most males were seen, 43%; most female patients were seen in the age group 40-49 years, 29%.

Pietinalho A, Hiraga Y, Hosoda Y, Löfroos A-B, Yamaguchi M, Selroos O. The frequency of sarcoidosis in Finland and Hokkaido, Japan. A comparative epidemiological study. Sarcoidosis 1995; 12:61-67 (29).The most recent epidemiological data on sarcoidosis in Finland comes from the work by Pietinalho et al. In 1984 they reported a prevalence of 28.2/10^5 and an annual incidence of 11.4/10^5. Among women the age-adjusted prevalence was highest in the age group 50-59 years, and among men in the age group 40-49 years. There was a female predominance with 63% of the patients being women.

Milman N, Selroos O. Pulmonary sarcoidosis in the Nordic countries 1950-1982. I. Epidemiology and clinical picture. Sarcoidosis 1990; 7:50-57 (30).

Milman and Selroos presented data from the Nordic countries. Patients were younger compared with the data by Pietinalho et al, but, as in most of the Nordic series a female predominance was noticed.

Sarcoidosis in children

Sarcoidosis in children and adolescents has seldom been detected in Finland. In a series of 140 patients Selroos found one female patient in the age group below 20 years (12). In the same age group below 20 years Elo found one male among 356 patients (18) and Pietinalho two females and one male among 334 patients (21).

Niemelä M, Uhari M, Repo H, Vuopala K. Pienen lapsen sarkoidoosi (Sarcoidosis in a young child). Duodecim 1999; 115:54-57 (in Finnish) (31)**.** Niemelä et al publiched a case history of a 6-month-old girl who developed skin lesions, arthralgia, iritis and hepato- and splenomegalia (26). Biopsy specimens of the skin, liver, spleen and of a salivary gland showed a granulomatous inflammation consistent with sarcoidosis. She was successfully treated with oral corticosteroids (and some methotrexate).

Organ-specific epidemiology data

Organ specific epidemiological sarcoidosis data from Finland has been published for uveitis in Northern Finland (32,33) and for cardiac sarcoidosis (34). These will be discussed later under organ specific headings.

Saari M, Miettinen R, Alanko H. Uveitis: report of a 10-year survey in Northern Finland. Can J Ophthalmol. 1975; 10:356-360 (32).

Karma A. Incidence of uveitis due to sarcoidosis in Northern Finland. Acta Ophthalmol (Copenh) 1979; 57:942 (33).

Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Ylitalo K, Kaikkonen K, Tuohinen S, Haataja P, Kerola T, Kokkonen J, Pelkonen M, Pietilä-Effati P, Utrianen S, Kupari M. Cardiac Sarcoidosis: Epidemiology, Characteristics and Outcome over 25 Years in a Nationwide Study. Circulation 2015 ; 131:624-632 (34).

Familiar occurrence of sarcoidosis

Selroos O, Sellergren T-L, Vuorio M, Virolainen M. Sarcoidosis in identical twins. Observations on the course of treated and untreated identical diseases. Am J Respir Dis 1973; 108:1401-1406 (35).
This report descibed sarcoidosis in identical twins. For family reasons these two young twins sisters had lived for appr. 15 years in different parts of the country without close contacts. Their mother had pulmonary tuberculosis at the time of their birth. The twins were diagnosed with identical diseases (pulmonary and ocular sarcoidosis) within the same calender year. One happened to be treated with oral corticosteroids, the other was left untreated. The follow-up showed a favourable and identical course in both patients.

Elo, in his thesis, reported a prevalence of familial sarcoidosis of 3.4% in the south-western district of Finland (18). Poukkala et al found a prevalence of 6% in an area in northern Finland (21).

Pietinalho A, Ohmichi M, Hirasawa M, Hiraga Y, Löfroos A-B, Selroos O. Familial sarcoidosis in Finland and Hokkaido, Japan – a comparative study. Respir Med 1999; 93:408-412 (36). A mapping of familial sarcoidosis in Finland (1955-1987) resulted in 56 familial cases with siblings and mother-child relations being the most prevalent. The cross-sectional occurrence of familial sarcoidosis was estimated to be 3.6%.

Grönhagen-Riska C, Fyhrquist F, Hortling L, Koskimies S. Familial occurrence of sarcoidosis and Crohn's disease. Lancet 1983; 1(8336):1287-1288 (37)**.** Grönhagen-Riska et al described a family in which both sarcoidosis and Crohn's disease occurred. Irrespective of disease all affected members of the family had the same HLA type (B8/DR3 – see below, genetic studies).

The clinical picture of sarcoidosis in Finland

At the time of diagnosis in the 1960's, approximately 50% of the patients had been asymptomatic, being detected via compulsory mass chest radiographic examinations for tuberculosis (12). Among patients

with symptoms, erythema nodosum was by far the most common sign of sarcoidosis, followed by fever and dyspnoea.

Putkonen T. Symptom complexes of beginning sarcoidosis. Arch Klin Exp Dermatol. 1966; 227:116-118. (In German) (38).

Hannuksela M. Kyhmyruusu (Erythema nodosum). Duodecim 1965; 81:1148-1151 (in Finnish) (39).

Putkonen and Hannuksela described in detail the early onset sarcoidosis with erythema nodosum and bilateral hilar lymphadenopathy – later known as Löfgren's syndrome. Putkonen, in 1966, noticed that among 157 patients with verified sarcoidosis, 45% of the cases had been detected by internists, 26% by chest physicians, 5% by dermatologists, 4% by ophthalmologists, and the rest by other specialists or general practicioners (38). Hannuksela reported that among 53 patients with erythema nodosum, 25 (22 women and three men, 47%) were due to sarcoidosis (39). Hannuksela also pointed out that since 1960's a variety of factors have been found to trigger erythema nodosum. Still, in 1986, sarcoidosis appeared to represent around 50% of all cases of erythema nodosum.

Selroos O, Pietinalho A, Löfroos A-B, Hellström P-E, Riska H. Sarcoidosis in Southern Finland 1981-1985. Sarcoidosis 1992; 9, suppl 1: 125-129 (40). Sixty-seven patients out of 147, 46%, (34 males, 33 females) had been detected symptom-free via screening procedures. Eighty patients (64% of the entire series) had been referred due to symptoms:

	No. of males (%)	No. of females (%)	Total
Total with symptoms	27 (34%)	53 (66%)	80 (100%)
Respiratory symtoms	19	34	53
Constitutional symptoms	12	23	35
Arthralgia	9	14	23
Erythema nodosum	5	17	22
Ocular symptoms	2	4	6
Enlarged peripheral lymphnodes	2	4	6
Skin lesions	2	1	3
Other symptoms	6	8	14

Mode of presenation

In the early 1960'ies sarcoidosis was still a poorly understood and an underdiagnosed disease. Chest radiographic changes were often misinterpreted as pulmonary tuberculosis. Erythema nodosum was not considered to be associated with sarcoidosis but mostly with tuberculosis or streptococcal infections.

At the 3rd international congress on sarcoidosis in Stockholm in 1963 (10) the term Löfgren's syndrome became well known to the participants. The syndrome consists of erythema nodosum, arthralgia and enlarged hilar/mediastinal lymph nodes. In 1965 to 1971 Putkonen and his group draw attention to erythema nodosum as an initial sign of sarcoidosis in Finland (13,38,39). In his series of 157 patients, 40% presented with erythema nosoum, 27% with chest radiographic manifestations, 12% with uveitis or parotitis, 9% with respiratory symptoms, 7% with skin lesions, and 5% with something else (38).

In the larger clinical series of patients with sarcoidosis (12,18,21) it was obvious that up to 50 per cent of patients with diagnosed sarcoidosis had been detected in a symptom-free stage – mostly via mass chest radiogarphic examinations for detection of tuberculosis. The compulsory chest X-ray examinations were discontinued in Finland in 1972. The most frequent findings among symptomatic patients were respiratory symptoms, erythema nodosum, arthralgia, fatigue and low grade fever. Ocular symptoms were rare (12), especially compared with findings in e.g. Japanese patients (21).

Pietinalho A, Ohmichi M, Hiraga Y, Löfroos A-B, Selroos O. The mode of presentation of sarcoidosis in Finland and Hokkaido, Japan. A comparative analysis of 571 Finnish and 686 Japanese patients. Sarcoidosis Vasc Diffuse Lung Dis 1996; 13:159-166 (41). Among patients with symptoms this survey showed the following: cough (33%), fever (21%), fatigue (21%), erythema nodosum (18%), dyspnea (18%), arthralgia (16%), and chest pain/chest tightness (12%). Five percent of the patients had ophthalmological symptoms. At the time of diagnosis the chest radiographic findings showed stage I disease in 48% of the cases, stage II in 39% and stage III in 12%. This percentage distribution between radio-

graphic stages had virtually not changed since the 1960's (12).

The acute type of sarcoidosis, Löfgren's syndrome, has represented around one third of all patients with erythema nodosum (12,13). In the 1960's patients with Löfgren's syndrome represented almost 50% of all patients diagnosed with sarcoidosis (12). Later studies have shown Löfgren's syndrome to form around 20% of all patients with newly diagnosed sarcoidosis (39). Extra pulmonary manifestations have represented only a minor part of the symptoms and signs at the time of diagnosis (12,18,21).

Forsén K-O, Pietinalho A, Selroos O. Sarcoidosis in the elderly. Sarcoidosis 1992; 9,suppl 1:477-478 (42). A study in elderly patients with sarcoidosis (age ≥65 years) showed that they represented 6.5% of all newly diagnosed patients. Sarcoidosis in elderly was also more prevalent among women (57%) compared with men. Compared with a patient group <65 years of age the elderly were more often diagnosed because of symptoms than the younger age group. However, the clinical picture did not differ between older and younger patients.

Putkonen T, Hannuksela M, Mustakallio KK. Cold season prevalence of the clinical onset of sarcoidosis. Arch Environ Health 1966; 12:564-568 (43).
Putkonen et al also described a cold season prevalence of sarcoidosis in Finland. In the 1960'ies Finland had relatively short and mild summer seasons but a cold season with snow from November to April. The clinical onset of sarcoidosis had its peak during this cold season. A seasonal onset of sarcoidosis with a peak in the months December to May was reported by Selroos (12).

Selroos O, Pietinalho A, Löfroos A-B, Hellström P-E, Riska H. Sarcoidosis in Southern Finland 1981-1985. Sarcoidosis 1992; 9, suppl 1: 125-128 (28). Sixty-seven patients out of 147, 46%, (34 males, 33 females) had been detected symptom-free via screening procedures. Eighty patients (64% of the entire series) had been referred due to symptoms:
The chest radiographic findings at referral were as follows:
In *symptom-free patients* stage I (14 men, 14 women, total 28), stage II (16 men, 15 women, total 31), stage III (4 men, 4 women, total 8).
In *patients with symptoms* stage I (16 men, 27 women, total 43), stage II (6 men, 15 women, total 21), Stage III (5 men, 10 women, total 14).
Taken together stage I was seen in 71 patients (48%), stage II in 52 (35%), and stage III in 23 (16%) patients.

The organ involvement in the 147 patients is summarized in the table:

Organ	No of patients, 147	Per cent
Intrathoracic lesions	146	99
Peripheral lymph nodes	52	35
Hypercalcaemia/-calciuria	50	34
Erythema nodosum	22	15
Eye lesions	15	10
Skin lesions	11	7
Liver involvement	11	7

Manifestations from the respiratory tract

Salmi I, Kava T. Vasemman ännihuulen halvaus – sarkoidoosin harvinainen ilmentymä (Paralysis of left vocal cord – an unusual finding in sarcoidosis). Duodecim 1993; 109:1951 (in Finnish) (44). The authors describe two patients with sarcoidosis and paralysis of nervus laryngealis recurrens. The patients had for sarcoidosis typically enlarged hilar and mediastinal lymph nodes. In one of the patients the paralysis remained irreversible, probably due to late treatment with corticosteroids. Nevertheless the described complication is rare in sarcoidosis. It is a more common complication in patients with lung cancer with mediastinal metastases.

Bronchial hyperresponsiveness and cough

Laitinen LA, Haahtela T, Kava T, Laitinen A. Non-specific bronchial reactivity and ultrastructure of the airway epithelium in patients with sarcoidosis and allergic alveolitis. Eur J Respir Dis 1983; 131 suppl: 267-284 (45). Airway hyperreactivity can be a transient phenomenon most frequently during the acute phase of sarcoidosis and lasting only for a few months. Laitinen et al postulated that areas of extensive epithelial damage, uncovering underlying afferent nerve endings of the bronchial mucosa,

was the mechanism of bronchial hyperresponsiveness in sarcoidosis, suggesting a neurogenic pathway.

Puolijoki H, Lahdensuo A. Causes of prolonged cough in patients referred to a chest clinic. Ann Med 1989; 21:425-427 (46). The study evaluated the causes of prolonged cough in a patient population referred to a chest clinic during a single year. One hundred and ninety-eight patients (11%) of the total yearly 1745 adult admissions fulfilled the criteria of prolonged cough. Asthma, suspicion of asthma and postnasal drip were the commonest causes of prolonged cough. Sarcoidosis was the cause of cough in 16% of the patients.

Selroos O, Löfroos A-B. Bronchial hyperresponsiveness in patients with pulmonary sarcoidosis. Eur Respir J 2010; 36, suppl:122s-123s (47). Data from, 168 patients with biopsy-verified pulmonary sarcoidosis was compiled regarding bronchial hyperresponsiveness (BHR) measured with a histamine inhalation challange test; stage I (n=90), stage II (n=69), stage III (n=6). When tested, BHR was present in 29% of the patients and equally prevalent in stage I and II. BHR was most frequent in patients with a short duration of disease; <2 years. Inhaled corticosteroids reduced BHR in 59 treated patients.

Chest X-ray	Disease duration	No of pts	BHR +	% positive BHR
Stage 0	<2 years	3	1	33
Stage I	<2 years	36	19	53
Stage I	>2 years	54	6	11
Stage II	<2 years	47	17	36
Stage II	>2 years	22	4	18
Stage III	>2 years	6	1	17
Total		168	48	29

Pleural involvement

Aho A, Heinivaara O, Mahonen H. Boeck's sarcoid as a cause of spontaneous pneumothorax. Ann Med Intern Fenn 1958; 47:163-167 (9). During a 6-year period the authors saw 32 patients with sarcoidosis. They reported three cases of spontaneous pneumothorax (9%). The patients were a 49-year old woman, and 30- and 47-years-old men. All three patients had radiographic pulmonary parenchymal infiltrates.

Selroos O. Exudative pleurisy and sarcoidosis. Br J Dis Chest 1966; 60:181-186 (48). Four cases of exsudative pleurisy were reported in patients with biopsy-verified sarcoidosis. A Kveim test was positive in two patients tested. In two patients the pleurisy was the first sign of disease. In the two other cases pleurisy developed in association with an exacerbation on sarcoidosis. Two of the patients were treated with corticosteroids; in the other two cases the pleural exsudate disappeared gradually without therapy. Elo, in his series of 158 patients, noticed pleural changes in 10 patients (2.8%) (18).

Diagnostic procedures

The diagnosis of sarcoidosis should be based on the clinical picture supported by a biopsy finding showing epithelioid cell granulomas and with exclusion of other granulomatous disorders (49). In the 1960'ies and 70'ies the Kveim-Siltzbach skin test was also used (12,13). The Kveim test was subsequently removed from the diagnostic arsenal due to difficulties in obtaining standardized test material and the risk of transmitting infectious agents via the material.

Kveim-Siltzbach test (in diagnostic work)

Putkonen showed a great interest in the Kveim test (3-7) and used it as the main diagnostic test. He and his group performed hundreds of tests. However, he never summarized, as far as this author knows, his final clinical experiences in this field. This may be due to the fact that he used material from lymph nodes and the obtained material from one patient was not enough to be used for standardization of the test material. However, Putkonen described that lymph node test material from a sarcoidosis patient who her/himself reacted weekly to the Kveim material resulted in a strong antigen, whereas on the contrary, material from a patient who reacted rapidly and strongly to Kveim material gave test material of low antigenicity (50).

Putkonen T. Source of potent Kveim antigen. Acta Med Scand Suppl. 1964; 176, suppl 425:83-85 (50).

In his thesis on erythema nodosum Hannuksela, working in Putkonen's department, reported that out of 161 patients with sarcoidosis and erythema nodosum the Kveim test was positive in 150 cases (93%) (13). It was typcal that the test became positive in the acute cases where diagnosis was reasonably easy to establish without Kveim's test. In more chronic, and may be more atypical cases, the Kveim test often remained negative (12,13).

For the work resulting in an academic thesis Selroos obtained Kveim test material from Siltzbach at the Mount Sinai hospital in New York (12). Kveim test was done in 96 cases. The test was positive in 22 of 23 patients (96%) with radiographic stage I and erythema nodosum, in 29 of 33 (87%) with stage I without erythema nodosum, in 25 of 37 (68%) with stage II and in none of 3 patients with stage III disease.

Biopsy studies

Peltokallio V, Peltokallio P. Liver needle biopsies and their complications with special reference to hemorrhages. Ann Med Intern Fenn 1963; 52:241-247 (51). The first study mentioning a biopsy procedure in sarcoidosis patients was published by Peltokallio and Peltokallio. They performed liver biopsies in patients with different diagnoses focusing on safety of the procedures. In a series of 176 liver biopsies in 168 patients they found a histopathological picture consistent with sarcoidosis in two cases. Selroos also reported two cases of positive liver biopsies in two patients with sarcoidosis (12) and Elo in three cases (18).

Selroos O. Biopsitagning vid olika stadier av lungsarkoidos (Obtaining biopsies of patients at different stages of pulmonary sarcoidosis) (in Swedish). Finska Läk-sällsk Handl 1968; 112:30-37 (52). The first study on biopsy procedures in patients with sarcoidosis and different chest radiographic stages was published already in 1968. The series consisted of 130 biopsy specimens from 90 patients. Fifty-two percent of the biopsies showed granulomas consistent with sarcoidosis. The best yield came from palpable lymph nodes (95% positive findings) followed by biopsies from the bronchial mucosa and the scalene nodes (Daniel's method) – both 50% positive findings. In patients with stage I chest radiographic findings 53% positive biopsies were seen; in stage II 46%. Of 50 biopsies of the bronchial mucosa, 10 out of 28 with stage I radiography, 14 of 20 with stage II, and one of two with stage III showed granulomas.

Havu M, Havu K, Juhola M, Kreus K-E. Maksabiopsia sarkoidoosin diagnostiikassa (Liver biopsy in the diagnosis of sarcoidosis). Suom Lääk L 1980; 35:513-515 (in Finnish) (53). Havu et al performed liver biopsies in 40 patients with sarcoidosis. In patients with intrathoracic lesions alone (n=27) granulomas in the liver were found in one patient of 10 with radiographic stage I, in five out of 15 with stage II, and in two patients of two with stage III. In 13 patients with extra pulmonary lesions in addition to intrathoracic lesions, five biopsies out of seven were positive in patients with intrathoracic stage I, and in five patients of six with stage II radiographic findings. In total, 45% of the liver biopsies showed granulomas consistent with sarcoidosis.

Mediastinoscopy

Mediastinoscopy as a diagnostic procedure in patients with suspected sarcoidosis was introduced in the 1960'ies. This procedure resulted in a high frequency (appr. 90%) of positive biopsy findings (54-58).

Pätiälä J. Observations on the significance of mediastinoscopy in the diagnosis of sarcoidosis. Acta Med Scand Suppl. 1964; 176 suppl 425:239-240 (54).

Palva T. Mediastinal sarcoidosis. Acta Otolaryngol 1964; 57 suppl 188:258-260 (55).

Koskinen O, Linden LW. Mediastinoscopy. In mediastinal surgery. Ann Otol 1964; 73:111-117 (56).

Palva T. Mediastinoskopia (Mediastinoscopy). Duodecim. 1969; 85:524-529 (in Finnish)(57).

Puhakka HJ, Liippo K, Tala E. Mediastinoscopy in relation to clinical evaluation. Scand J Thorac Cardiovasc Surg. 1990; 24:43-45 (58).

Puhakka et al (58) evaluated the entire spectrum of mediastinoscopy, from common to rare conditions,

in relation to clinical judgement. The 2021 consecutive patients comprised 992 with 'open' clinical diagnoses at mediastinoscopy and 1029 with verified or presumptive diagnoses. In the first group the most common indications for mediastinoscopy were pulmonary infiltrates (73%) and mediastinal shadows (17%), and in the second group bronchogenic carcinoma (57%) and sarcoidosis (38%). Mediastinoscopy was classified as positive in 43% of the first, and in 60% of the second group. Of the total series, 51% had positive mediastinoscopy findings, the most common being malignant disease (24%) and sarcoidosis (21%). Mediastinoscopy was useful especially for evaluating malignant mediastinal involvement, but also for differentiation of lymphadenopathies and in diagnosis of rare diseases.

Elo, in his academic thesis reported on 136 mediastinoscopies in patients with suspected sarcoidosis (18). The biopsies were diagnostic for sarcoidosis in 132 cases (97%). However, the procedure required general anaesthesia and left patients with an often unsightly scar.

Biopsies of the lung parenchyma

In the 1970'ies clinicians started to obtain biopsies of the lung parenchyma.

Tukiainen P, Taskinen E, Korhola O, Valle M, Maasilta P. TruCut needle biopsy in sarcoidosis. Relationship between histology of the biopsy specimens and radiographic features and pulmonary function. Br J Dis Chest 1983; 77:243-248 (59).
This biopsy procedure was done with the TruCut needle (14,59) or as an open surgical procedure (59,60). Tukiainen et al (59) performed ninety-nine TruCut needle biopsies on 92 patients with sarcoidosis. Non-caseating granulomas were found in 77 of 92 patients (84%) and in 78 of 99 biopsies (79%). Granulomas were found in 67% of patients showing only slight radiographic opacity (ILO classification grades 00-11) and in 90% of patients with higher radiographic grades (ILO 12-33). There was also a positive relationship between the size of the biopsy specimen and the presence of granulomas. Granulomas were found in 68% of small biopsy specimens and in 90% of moderate or large specimens.

Laustela E, Ala-Harja K, Tala P. Surgical lung biopsy in diffuse pulmonary disease. Scand J Respir Dis. 1967; 48:156-166 (60). Laustela et al reported the results of open lung biopsies in 37 patients with radiographic pulmonary and/or mediastinal abnormalities but without a firm diagnosis despite several other procedures. Sarcoidosis was found in four of the 37 cases. It appeared to the authors that the diagnosis of sarcoidosis can be obtained in easier ways than via open lung biopsies.

Laustela E, Ala-Harja K. The value of biopsy procedures in diagnosis of intrathoracic sarcoidosis. Ann Chir Gynaec Fenn 1968; 57:485-487 (61). Laustela and Ala-Harja reported these biopsy findings in a series of 54 patients with verified intrathoracic sarcoidosis. The scalene lymph noded biopsy showed granulomas in 27 of 40 cases, bronchoscopy in 11 of 28 cases, mediastinoscopy in 13 of 13 cases, needle liver biopsy in five of ten cases, skin biopsy in three cases, and open lung biopsy in one case.

Bronchoscopy

Palojoki A. Diagnosis in sarcoidosis. How many biopsies with bronchoscopy. In: Bronchology, research and therapeutic aspects. (eds. JA Nakhosteen, W Maassen). 1981, pp. 195-197 (62).
Palojoki pointed out that at obtaining several biopsies of the bronchial mucosa significantly increases the possibility to obtain samples with granulomas in patients with suspected sarcoidosis.

Palojoki A. Diagnostic yield of bronchial mucosal biopsy with the bronchofiberscope. Panminerva Med 1986; 28:253-254 (63). In a series of 87 patients (136 biopsies of the bronchial mucosa; 1.6 samples per patient) only 57 (65.5%) were diagnostic and 30 were "poor" (34.5%). The rest were non-diagnostic or too small.

Elo performed 350 bronchoscopies in patients with verified sarcoidosis (18). Granulomas were found in 150 cases (43%): 20 positive findings in 87 patients with radiographic stage I disease, 123 positive biopsies in 252 patients (49%) with stage II, and 7 out of 12 in patients with stage III disease. Elo also reported on 30% positive biopsies in 27 patients using transbronchial puncture.

Halme M, Piilonen A, Taskinen E. Comparison of endobronchial and transbronchial biopsies with high-resolution CT (HRCT) in the diagnosis of sarcoidosis. APMIS 2001; 109:289-294 (64).
Halme et al performed endobronchial and transbronchial biopsies in a series of 45 patients with suspected sarcoidosis. A total of 35 patients were diagnosed as having sarcoidosis. All but three had parenchymal infiltrates on high resolution computed tomography. Bronchoscopy with lavage, endobronchial and transbronchial biopsies was performed. Endobronchial biopsies showed granulomas in 24% and transbronchial biopsies in 50% of the cases. All patients had lymphocytosis in their bronchoalveolar lavage fluid samples.

Fine-needle aspiration biopsies

Lymph nodes

Lohela P, Tikkakoski T, Strengell L, Mikkola S, Koskinen S, Suramo I. Ultrasound-guided fine-needle aspiration cytology of non-palpable supraclavicular lymph nodes in sarcoidosis. Acta radiol 1996; 37:896-899 (65). Lohela et al performed ultrasound-guided fine-needle aspiration biopsies of non-palpable lymph nodes in patients with suspected sarcoidosis. Of a total of 250 patients, 27 (10.8%) had enlarged supraclavicular lymph nodes at ultra sound examination. All these were non-palpable at clinical examination. The cytological specimen was quantitatively sufficient in 25 of the 27 cases (93%). In 22 (88%) of these, the cytological diagnosis was granulomatous inflammation suggestive of sarcoidosis. The patients were followed for 2-42 months (mean 19 months), and the diagnosis of sarcoidosis was confirmed clinically in all cases.

Klemi PJ, Elo JJ, Joensuu H. Fine needle aspiration biopsy of granulomatous disorders. Sarcoidosis 1987; 4:38-41 (66).

Elo JJ, Joensuu H, Klemi PJ. Fine needle aspiration biopsy of granulomatous disorders. In: Sarcoidosis and other granulomatous disorders (eds. C Grassi, G Rizzato, E Pozzi). Elsevier Science Publ, Amsterdam, 1988, pp.515-516 (67). Klemi et al performed fine-needle aspiration biopsies on 21 patients with palpable lymph nodes or parotid glands. Five patients had biopsy verified sarcoidosis. They concluded that fine-needle aspiration was a practical and reliable method to diagnose granulomatous disorders.

Spleen

Selroos O. Fine-needle aspiration biopsy of spleen in diagnosis of sarcoidosis. Proc NY Acad Sci 1976; 278:517-519. (68). Selroos introduced fine-needle aspiration biopsy of the spleen as a diagnostic procedure in patients with suspected sarcoidosis. This was a safe procedure as long as the patients' platelet cound and the bleeding time were normal.

Selroos O. Sarcoidosis of the spleen. Acta med scand 1976; 200:337-340 (69).

Selroos O.Fine-needle aspiration biopsy of spleen in diagnosis of sarcoidosis. Z Erkrank Atm-Org 1977; 149:109-111 (70).

Selroos O, Koivunen E. Usefulness of fine-needle aspiration biopsy of spleen in diagnosis of sarcoidosis. Chest 1983; 83:193-195 (71). In these later reports in larger number of patients – the largest material consisted of 557 evaluable aspirations (71) – splenic granulomas were found in 57 per cent of patients with radiographic stage I disease and in 61 per cent in patients with stage II. In 2 of 8 patients with stage III findings granulomas were found.

Taavitsainen M, Koivuniemi A, Helminen J, Bondestam S, Kivisaari L, Pamilo M, Tierala E, Tiitinen H. Aspiration biopsy of the spleen in patients with sarcoidosis. Acta radiol 1987; 28:723-725 (72).

A subsequent study by Taavitsainen et al revealed a positive fine-needle biopsy finding in 19 of 79 patients (24%) with sarcoidosis. Three minor complications occurred.

Myocardium

Lehtonen JY, Jokinen JJ, Holmström M, Kupari M. Open-chest core needle biopsy of the left ventricle in the evaluation of suspected focal myocardial inflammation. J Thorac Cardiovasc Surg

2015; 149:e99-102 (73)**.** Compared with standard myocardial biopsies, which may give a diagnosis of myocardial sarcoidosis in 20% by its best, Lehtonen et al described the advantage of open-chest core needle biopsies of the left ventricle in the evaluation of suspected focal myocardial inflammation. They presented three patients where open-chest core biopsy had verified the diagnosis.

Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) was introduced as a research tool in pulmonary medicine In the early 1980'ies. Although sarcoidosis was characterized by an increase in BAL lymphocytes, and among them predominantly in T-helper (CD4) lymphocytes, the cellular picture was not diagnostic for sarcoidosis. However, recovery with or without treatment was paralleled by a normalization of lymphocyte count in the BAL fluid. The first BAL studies in Finland in patients with sarcoidosis aimed at studying the influence of corticosteroid treatment on BAL cell counts, and biochemical markers in serum and BAL.

Erkkilä S, Fröseth B, Hellström P-E, Kaltiokallio K, Taskinen E, Viljanen A, Viljanen B, Selroos O. Inhaled budesonide influences cellular and biochemical abnormalities in pulmonary sarcoidosis. Sarcoidosis 1988; 5:106-110 (74). The authors performed a placebo-controlled study in 19 patients with newly detected pulmonary sarcoidosis. Patients were treated for 8 to 10 weeks and bronchoalveolar lavage (BAL) was performed before and after treatment with inhaled budesonide, 800 μg twice daily. In addition to cell findings also angiotensin converting enzyme (ACE), β_2-microglobulin (β_2M), albumin and hyaluronic acid were measured in BAL fluid. Serum ACE and β_2M were measured, too. A decrease in BAL lymphocytes and in T-helper/T-suppressor cell ratio, and in BAL hyaluronan concentration was found in the budesonide-treated group compared with the placebo group. Serum ACE and β_2M also decreased significantly.

Prior C, Barbee RA, Evans PM, Townsend PJ, Primett ZS, Fyhrquist F, Grönhagen-Riska C, Haslam PL. Lavage versus serum measurements of lysozyme, angiotensin converting enzyme and other inflammatory markers in pulmonary sarcoidosis. Eur Respir J 1990; 3:1146-1154 (75). Fyhrqvist and Grönhagen-Riska, in collaboration with the National Heart and Lung Institute in London, counted cells and measured A CE and lysozyme (LZM) in BAL fluid in 25 patients with pulmonary parenchymal sarcoidosis. Patients were treated with prednisolone for a median of 13 months (range 3-49 months). No placebo group was included. The BAL lymphocyte count was the best predictive marker of radiographic response to corticosteroids. Serum lysozyme levels appeared to be a more useful marker of overall disease activity than measurements of other inflammatory markers.

Taskinen E, Tukiainen P, Renkonen R. Bronchoalveolar lavage. Influence of cytological methods on the cellular picture. Acta Cytol 1992; 36:680-686 (76).

Taskinen EI, Tukiainen PS, Alitalo RL, Turunen JP. Bronchoalveolar lavage. Cytological techniques and interpretation of the cellular profiles. Pathol Annu. 1994; 29 (Pt 2):121-155 (77). Taskinen et al published studies comparing different bronchial lavage methods and their influence on the cellular picture and the diagnostic value of the cell counts in patients with interstitial lung diseases, including sarcoidosis.

Tukiainen P, Taskinen E, Riska H. The prognostic value of bronchoalveolar lavage in sarcoidosis. Sarcoidosis. 1994; 11:69-72 (78). Tukiainen et al. studied a total of 237 sarcoidosis patients with a sufficiently long follow-up period. Those with complete remission had been followed for at least one year (32±13 months; mean ±SD) and those without complete remission for 45±13 months. They found that a high CD8+ T-suppressor cell count and to a lesser extent a low CD4+/CD8+ cell ratio (T helper/T suppressor cell ratio) related to an unfavourable prognosis. A high ratio and high CD4+ T cell proportion related to a good prognosis (as in previous international studies). Using step-wise logistic regression analysis they furthermore found that erythema nodosum, age below 50 years, IgG ≤40 g/l in BAL fluid and few diffuse radiographic opacities were associated with a good prognosis.

Pietinalho A, Sutinen S, Fröseth B, Linko L, Backman R, Riska H. Cytology and soluble contents in

alveolar lavage fluid (ALF) as signs of activity in untreated sarcoidosis. Sarcoidosis 1994; 11:87 (79). Pietinalho et al focused on soluble contents in BAL fluid as sign of activity in untreated sarcoidosis. They studied 19 healthy control subjects and 34 untreated sarcoidosis patients with a duration of symptoms of less than 3 months (n=11, group 1), at least 3 months but less than 1 year (n=12, group 2), and for more than 1 year (n=6, group 3). They reported total cell counts (TC), proportion of lymphocytes (Ly%), the content of total protein (TP), albumin (A), immunoglobulins (IgA, IgG, IgM), hyaluronic acid (HA), procollagen-3 peptide (PCP), and β_2-microglobulin (BM). Compared with healthy controls, TC and Ly% were elevated in groups 1 and 2, but not in group 3. TP, A, IgG, HA and PCP were increased in all three groups, IgA was elevated in groups 2 and 3, and IgM in group 3. BM was elevated in groups 1 and 2. Comparisons between the groups indicated that an increased secretion of many soluble contents of BAL persists longer than lymphocytosis in untreated sarcoidosis patients. The reference values used in this study were published by Sutinen et al (80).

Sutinen S, Riska H, Backman R, Sutinen SH, Fröseth B. Alveolar lavage fluid (ALF) of normal volunteer subjects: cytologic, immunocytochemical, and biochemical reference values. Respir Med 1995; 89:85-92 (80).

Wolff H, Teppo AM, Mutanen P, Sutinen S, Backman R, Sutinen S, Pietinalho A, Riska H. Studies of cytokine levels in bronchoalveolar fluid lavage from patients with interstitial lung diseases. Scand J Clin Lab Invest. 2003;63:27–36 (81). The concentration of cytokines in lavage fluid has also been reported in patients with pulmonary sarcoidosis and other interstitial lung diseases. So far these determinations have not reached routine clinical applications but may be of importance in the future.

Lymphography

Wiljasalo M, Tani P. Thoracic sarcoidosis and lymphography. Scand J Respir Dis 1968; 65, suppl 251-257 (82).

Tani P. Lymphografie bei Sarkoidose. Z Erkr Atmungsorgane Folia Bronchol. 1970; 133:470-472 (83). In the 1960'ies lymphography was introduced as a diagnostic tool in clinical medicine. In 1968 Wiljasalo and Tani published a paper illustrating enlarged lymph nodes compatible with sarcoidosis. The method did not reach any significant popularity as other methods were developed.

Granulomas mimicing sarcoidosis

Venho KK, Selroos O, Haahtela T, Mönkäre S. Splenic granulomas in farmer's lung disease. An extrapulmonary manifestation of extrinsic allergic alveolitis. Acta med scand 1982; 211:413-414 (84). The authors reported the results of splenic fine-needle aspiration biopsies in 10 patients with allergic alveolitis. In five of the 10 patients with acute or subacute disease granuloma-like lesions were seen in the aspirates.

Reijula K, Sutinen S, Tuuponen T, Lahti R, Kärkölä P. Pulmonary fibrosis, with sarcoid granulomas and angiitis, associated with handling of mouldy lichen. See comment in PubMed Commons belowEur J Respir Dis. 1983; 64:625-629 (85). The authors reported a case of extrinsic allergic bronchiolo-alveolitis associated with handling of mouldy lichen. The patient had periodic dyspnoea, cough and mucoid sputum, and a micronodular infiltration of both lungs with slight restrictive ventilatory insufficiency. An open lung biopsy showed interstitial inflammation and fibrosis with sarcoid granulomas and angiitis. The symptoms disappeared during long-term corticosteroid therapy, but reappeared every year when the patient participated in the handling of lichen (Cladonia alpestris). Precipitating antibodies against Aspergillus fumigatus, A. umbrosus, and Thermoactinomyces vulgaris, were detected in the patient's serum, and against a mixture of fungi including A. terreus, Rhizopus spp., Cladosporium spp., and Penicillium spp., isolated from mouldy lichen storage boxes. After retirement, the patient's symptoms disappeared and the lung function tests showed a slight improvement. In Northern Finland, farmers generally participate in lichen collection. Antigens from mouldy hay and from mouldy lichen may represent a double occupational hazard for them.

Tukiainen P, Nickels J, Taskinen E, Nyberg M. Pulmonary granulomatous reaction: talc pneumoconiosis or chronic sarcoidosis? Br J Ind Med. 1984; 41:84-87 (86). A chronic pulmonary granulomatous reaction was associated with an almost identical clinical picture in two patients exposed to talc. In both patients lung biopsy showed the deposition of talc particles and a heavy granulomatous reaction. At the time of diagnosis the Kveim test result was negative in both patients, urinary calcium excretion was normal, and there were no extrapulmonary manifestations and no response to steroid treatment. These findings point against sarcoidosis. The serum angiotensin-converting enzyme level, however, was raised in both patients. It was concluded that the patient who was exposed to talc in the rubber industry had a true talc pneumoconiosis. The other patient, who was exposed to cosmetic talcum powder, suffered from chronic sarcoidosis with talc deposition in the lungs, since an enlarged axillar lymph node containing granulomatous inflammation was discovered after two years' follow up. These cases show that it may be extremely difficult to differentiate between chronic sarcoidosis and talc pneumoconiosis even after careful clinical and histological analysis.

Biochemical markers of disease activity

In the mid 1960'ies Putkonen and his group became interested in immunological alterations in relation to the development of a positive Kveim test.

Putkonen T, Jokinen EJ, Mustakallio KK. Unusual immunologic alterations in sarcoidosis during repeated Kveim testing. Am J Med 1965; 39:985-993 (87). In ten patients with sarcoidosis Kveim tests were repeated within five weeks, using the most potent Kveim antigen. In three of the patients, the response to the second Kveim test was weaker than the first, in six similar to the first, but in one markedly stronger . This latter patient exhibited other unusual immunologic alterations during the Kveim testing period, including a biologic false-positive flocculation reactions for syphilis and complement-fixing serum activity against the repeatedly tested Kveim antigens . Moreover, bodies identified as pine pollen were found in the sarcoid lymph nodes.

Mustakallio KK, Vuopio P, Videman T, Venesmaa P, Putkonen T. Immunoglobulins, haptoglobin, and transferrin in sarcoidosis in relation to patients' Kveim reactivity and stage of the disease. Ann Med Intern Fenn 1967; 56:19-21 (88). Putkonen's group also analyzed immunoglobulins, haptoglobin and transferrin concentrations in serum in 43 patients with subacute and in eight with chronic sarcoidosis. The patients with Löfgren's syndrome and a positive Kveim test showed a tendency to increase in haptoglobin and IgM. When an involvement of the lungs became apparent, IgA and IgG often showed an increase and transferrin sometimes a decrease. Later on, in the regressive or chronic stage of sarcoidosis IgM, IgA and IgG decreased, and in that order, approaching the normal reference levels.

Uitto J, Tani P, Pihko H. Clinical significance of urinary and serum hydroxyproline determination in sarcoidosis. Clin Chim Acta 1971; 32:265-269 (89). In 88 patients with sarcoidosis urinary excretion of total hydroxyproline and serum free hydroxyproline concentration were determined. 217 and 95 control subjects served as controls. The results indicated that slightly increased values can be observed for urinary excretion of hydroxyproline and for serum free hydroxyproline in sarcoidosis, but these changes are of little significance if any in the diagnosis or clinical evaluation of the disease process.

Palva T, Raunio V, Nousiainen R. Lactate, malate and glutamate dehydrogenase activity in mediastinal lymph nodes in sarcoidosis. Ann Clin Res 1972; 4:223-227 (90).

Palva T, Dammert K, Palva A. On enzyme histochemistry of sarcoidosis. Acta Pathol Microbiol Scand (A) 1973; 81:1898-194 (91).

Palva T, Raunio V, Nousiainen R. Alkaline and acid phosphatase activity in sarcoid lymph nodes. Acta Pathol Microbiol Scand (A) 1973; 81:577-582 (92). Palva et al studied enzyme histochemistry in lymph nodes obtained at mediastinoscopy of patients with sarcoidosis. Among enzymes studied were glutamate dehydrogenase, alkaline and acid phosphatase activities. The series of patients was too limited in order to claim diagnostically useful endpoints. Nevertheless, these studies indicated that measurements

of enzymes in the future, and may be from the more easily accessible sites than lymph nodes, e.g. serum, might be of clinical importance.

Anttinen H, Terho EO, Järvensivu PM, Savolainen ER. Elevated serum galactosylhydroxylysyl glucosyltransferase, a collagen synthesis marker, in fibrosing lung diseases. Clin Chim Acta 1985; 148:3-8 (93). The activity of galactosylhydroxylysyl glucosyltransferase, an enzyme catalyzing collagen biosynthesis, was measured in the sera of 101 patients with various pulmonary diseases to study whether detectable enzyme amounts are liberated into the serum from the lung tissue, and whether this is associated with the development of lung fibrosis. Increased serum galactosylhydroxylysyl glucosyltransferase activity was found in all the patients with progressive pulmonary fibrosis and in about half of the patients with acute stages of farmer's lung and infectious pneumonia. In one third of the patients with stage I sarcoidosis the serum enzyme activity was slightly increased, whereas in bronchial asthma and chronic bronchitis the values were mostly within the normal range. Elevated serum enzyme activity was thus demonstrated in connection with those respiratory diseases in which pulmonary fibrosis was already verifiable or relatively often develops later.

Lysozyme

The first test in sarcoidosis to be clinically useful was the measurement of serum lysozyme concentrations. Klockars, during his post doc period in Elliot Osserman' s lab at Columbia University in New York, had gained expertice in the lysozyme field. Lysozyme concentrations were measured with the lysoplate method with human lysozyme as standard.

Selroos O, Klockars M. Serum lysozyme in sarcoidosis. Evaluation of its usefulness in determination of disease activity. Scand J Respir Dis 1977; 58:110-116 (94). Serum lysozyme (LZM) determinations were peformed in 84 patients with clinically proven sarcoidosis. All patients were normocalaemic and had a normal renal function. An increased LZM activity was demonstrated in patients with pulmonary stage I and stage II disease, as well as in patients with extrapulmonary lesions. Treatment with corticosteroids rapidly normalized the LZM activity. A normal LZM activity was found in patients with cured sarcoidosis. The serum LZM activity seemed to reflect the total mass of biologically active granulomas and was of great value in determining the activity of the disease. The dosage of corticosteroids can probably be administered according to the actual LZM level. Increasing LZM activity after stopping treatment may indicate progressive and uncured disease. Normal LZM activity in patients with even large pulmonary lesions seemed to indicate inactive disease and unresponsiveness to treatment.

Klockars M, Selroos O. Immunohistochemical demonstration of lysozyme in the lymph nodes and Kveim reaction papules in sarcoidosis. Acta path microbiol scand Sect A 1977; 85:169-173 (95). The origin of lysozyme in serum was apparently sarcoid granulomatous tissue as histochemical studies showed its presence in abundance in macrophages in lymph nodes and Kveim test papules of patients with elevated concentrations in serum.

Koivunen E, Grönhagen-Riska C, Klockars M, Selroos O. Blood monocytes and serum and bone marrow lysozyme in sarcoidosis. Acta med scand 1981; 210:107-110 (96). Koivunen et al studied blood monocytes, lysozyme concentrations and angiotensin converting enzyme (ACE) activity in 88 sarcoidosis patients. In patients with an increased activity of serum ACE a positive correlation was seen between blood monocytes and serum lysozyme concentrations, but not in patients with normal ACE activity. They also studied blood and bone marrow lysozyme in 10 sarcoidosis patients. Lysozyme was found in bone marrow plasma and serum in a ratio of 1.5 to 1. They postulated that the positive correlation between blood monocytes and lysozyme in sarcoidosis patients might be due to recruitement of bone marrow monocytes for granuloma formation.

Later on several studies delt with simultaneous determinatrion of lysozyme, angiotensin-converting enzyme, β_2-microglobulin, adenosine deaminase and soluble interleukin 2 receptor (see below).

Angiotensin converting enzyme (ACE)

In 1975 Lieberman described increased activity of angiotensin-converting enzyme in patients with sar-

coidosis. Fyhrqvist, Grönhagen-Riska et al. developed a new assay for measurement of angiotension-converting enzyme (ACE) in serum (97), and later on new assays and modifications for ACE measurements in cerebrospinal fluid (CSF) and tears (98,99).

Fyhrqvist F, Tikkanen I, Grönhagen-Riska C, Hortling L, Hichens M. Inhibitor binding assay for angiotensin-converting enzyme. Clin Chem 1984; 30:696-700 (97).

Oksanen V, Fyhrqvist F, Somer H, Grönhagen-Riska C. Angiotensin converting enzyme in cerebrospinbal fluid :a new assay. Neurology (NY) 1985; 35:1220-1223 (98).

Immonen I, Friberg K, Sorsila R, Fyhrquist F. Concentration of angiotensin-converting enzyme in tears of patients with sarcoidosis. Acta Ophthalmol (Copenh). 1987; 65:27-29 (99).

Oksanen et al measured serum and cerebrospinal fluid (CSF) ACE by a new inhibitor binding assay in 32 patients with sarcoidosis, 49 with neurologic diseases, and 38 controls. In neurosarcoidosis, 11 of 20 patients had high levels of CSF ACE (98). In systemic sarcoidosis without neurologic abnormality, only 1 of 12 patients had elevated CSF ACE. The highest value was observed in a patient with widespread meningeal sarcoidosis. High values were also observed in patients with bacterial meningitis or malignant tumors of the CNS. Fluctuation in successive analyses correlated to clinical course of neurosarcoidosis. CSF ACE analysis seemed useful in diagnosis and follow-up of neurosarcoidosis. Immonen et al also studied the concentration of angiotensin-converting enzyme (ACE) in tears in 39 patients with sarcoidosis, 6 of them had active uveitis, 7 patients with non-sarcoid uveitis and 36 healthy controls (100). ACE concentration in tears was also compared with total protein concentration in tears in order to exclude the effect of varying dilution of tears at sampling. Mean tear ACE concentration and ACE/protein ratio were higher in patients with sarcoidosis than in controls. There were no significant differences in tear ACE concentration or ACE/protein ratio between sarcoidosis patients with uveitis and those with no eye involvement. Tear ACE concentration and ACE/protein ratio did not correlate significantly with serum ACE concentration. It was concluded that the mean concentration of tear ACE and ACE/protein ratio are elevated in sarcoidosis, but that this elevation is independent of any eye involvement.

Immonen I, Friberg K, Grönhagen-Riska C, von Willebrand E, Fyhrquist F et al. Angiotensin-converting enzyme in sarcoid and chalazion granulomas of the conjunctiva. Acta Ophthalmol (Copenh) 1986; 64:519-521 (100). Angiotensin-converting enzyme (ACE) was studied immunohistochemically in conjunctival biopsies from 6 patients with systemic sarcoidosis, 4 patients with posterior non-sarcoid uveitis and in specimens from 4 patients with chalazion of the eyelid. Specimens with sarcoid granulomas showed intense ACE-positive immunoreactivity in epithelioid cells of the granuloma, whereas chalazion granulomas did not contain ACE-immunoreactivity. There was no difference in staining patterns between specimens without granulomas. Thus immune-histochemical staining for ACE may be of help in differentiating conjunctival granulomatous tissue of a chalazion from sarcoid granuloma and lung tissue.

Grönhagen-Riska et al. published a series of papers dealing with the clinical usefulness of measuring ACE activity in serum of patients with sarcoidosis (101-107). They found that serum ACE was independent of age, sex and smoking habits. Healthy children as a group had higher ACE activity than healthy adults. Patients with clinically active sarcoidosis had higher ACE activity than patients with clinically inactive disease. The duration of disease did not affect the ACE levels. Sarcoidosis patients with acute disease with erythema nodosum usually had normal ACE activity. ACE activity seemed to correlate with the degree of pulmonary lesions and not as much with the presence of extrapulmonary manifestations. Treatment with oral corticosteroids decreased quite rapidly the ACE serum levels both in sarcoidosis patients and in controls. Repeated measurements of serum ACE seemed to correlate with the clinical development of the disease although exceptions were seen. In general, measurement of serum ACE was recommended as a marker of disease activity in untreated sarcoidosis. Increased activity during treatment with corticosteroids seemed to indicate a too low dose of the corticosteroid.

Grönhagen-Riska C. Angiotensin-converting enzyme. I. Activity and correlation with serum lysozyme in sarcoidosis, other chest or lymph node diseases and healthy persons. Scand J Respir Dis 1979; 60:83-93 (101). Serum angiotensin-converting enzyme (ACE) activity was studied in healthy controls, in 57 untreated sarcoidosis patients, and in 164 patients with other chest or lymph node diseases. The serum ACE activity of healthy persons was independent of sex, intake of meals, and smoking habits. There were no diurnal variations. Healthy children had a significantly higher ACE mean value than adults, whose ACE activity was not affected by age. The sarcoidosis patients had the highest ACE mean values, but those of patients with silicosis and asbestosis were also significantly elevated. Pulmonary cancer patients had decreased serum ACE activity, which was probably due to antimitotic treatment. Serum lysozyme (LZM) concentrations did not correlate with normal ACE activity, but the correlation between elevated ACE and LZM was significant in sarcoidosis and silicosis, and the trend was clearly the same for asbestosis. This indicated separate sources for these enzymes when ACE activity is normal, and a common source, i.e. macrophages, when ACE activity is increased.

Grönhagen-Riska C, Selroos O, Wägar G, Fyhrquist F. Angiotensin-converting enzyme. II. Serum activity in early and newly diagnosed sarcoidosis. Scand J Respir Dis 1979; 60:94-101 (102). Serum angiotensin-converting enzyme (ACE) was studied in 51 patients with early or newly diagnosed sarcoidosis. Only 45% of these patients had increased ACE activity when their diagnosis was established, which diminished the diagnostic value. On the other hand, ACE accurately reflected disease activity, and it proved a useful tool for assessing of need for corticosteroid treatment. Patients with acute sarcoidosis associated with erythema nodosum (EN) had low ACE activity compared with the other patients with active, but less acute disease. Serum ACE was not significantly correlated with blood lymphocytes or the immunoglobulins, but there was a positive correlation between the enzyme and serum lysozyme, which strengthend the hypothesis of both enzymes being produced by the epithelioid cells of sarcoid granulomas.

Selroos O, Grönhagen-Riska C. Angiotensin converting enzyme. III. Changes in serum level as an indicator of disease activity in untreated sarcoidosis. Scand J Respir Dis 1979; 60:328-336 (103). The activity of serum angiotensin converting enzyme (ACE) was repeatedly measured together with serum lysozyme (LZM) in patients with untreated sarcoidosis. Changes in the clinical picture were registered using chest radiographs, forced vital capacity (FVC), diffusing capacity for carbon monoxide (DL_{CO}) and appearance of extrapulmonary lesions. During a clinically unchanged period the highest ACE activity and the corresponding LZM value (not the highest value) were used for the calculation. A statistically significant change in ACE was noted when a normal chest radiograph changed to a stage II lesion or vice versa, and when a signficant change in FVC occurred. All other changes were insignificant. On the other hand, statistically significant changes in ACE were found during stable periods according to chest radiograph, FVC or DL_{CO}. ACE was frequently elevated in serum of patients with active sarcoidosis. The fluctuations in activity mostly parallelled the clinical course of the disease. An increased concentration of serum LZM was frequent in patients with active sarcoidosis. The highest LZM values were not always seen simultaneously with the highest ACE values, indicating that they probably expressed different dimensions of the disturbances in the sarcoid granuloma.

Grönhagen-Riska C, Selroos O. Angiotensin converting enzyme. IV. Changes in serum activity and in lysozyme concentrations as indicators of the course of untreated sarcoidosis. Scand J Respir Dis 1979; 60:337-344 (104). The mean values of serum angiotensin-converting enzyme (ACE) activities and lysozyme (LZM) concentrations measured during different phases of sarcoidosis coincided well with the clinical evaluation of the state of the disease. However, both enzymes, especially LZM, decreased before improvement was detected. Changes in ACE and LZM were in accord with the simultaneous clinical development in three fourths of the cases. Incompatibility between clinical observations and LZM fluctuations was most frequently seen during active stable or inactive disease. LZM often decreased during the active stable phase and fluctuated irregularly during inactive disease. During the former phase LZM decrements possibly reflected decreasing

activity of granulomatous macrophages and, in fact, preceded detectable improvement. ACE changes parallelled the clinical development more often than corresponding LZM changes during stable sarcoidosis. This may have been misleading and due to a delayed reaction of serum ACE, compared with LZM, in reflecting the activity of granulomatous cells. This delayed reaction was also observed in connection with erythema nodosum. Stable ACE activity during inactive sarcoidosis indicated the usefulness of measurements when trying to predict a relapse.

Grönhagen-Riska C, Selroos O, Niemistö M. Angiotensin converting enzyme. V. Serum levels as monitors of disease activity in corticosteroid-treated sarcoidosis. Eur J Respir Dis 1980; 61:113-122 (105). Serum angiotensin-converting enzyme (ACE) activity was related to clinical markers of disease activity, mainly chest radiographs, pulmonary function tests and serum lysozyme (LZM) in 41 sarcoidosis patients, who received corticosteroid treatment. Increased ACE activity before treatment predicted improvement of diffusion capacity during treatment, whereas chest radiographs improved regardless of the initial ACE value. ACE decreased after initiation of treatment both in sarcoidosis patients and in healthy volunteers. In sarcoidosis most decreases were parallelled by similar LZM changes, which did not occur in volunteers. When an apparently stable state had been achieved, ACE was no longer a reliable monitor of disease activity. It often fluctuated within normal limits without accompanying clinical or LZM changes. It was not dose-dependent during daily medication but increased during alternate day administration. This may have reflected decreased suppression of ACE by steroids but may also have indicated reactivation of the disease process. Elevated ACE values after cessation of treatment preceded or parallelled a relapse. LZM values did not add to the information provided by ACE measurements before, during or after treatment.

Grönhagen-Riska C, Kurppa K, Fyhrquist F, Selroos O. Angiotensin-converting enzyme and lysozyme in silicosis and asbestosis. Scand J Respir Dis 1978 ; 59:228-231 (106).

Grönhagen-Riska C, Selroos O, Fröseth B, Fyhrqvist F, Hellström P-E, Kurppa K, Wägar G. Increased serum angiotensin converting enzyme (ACE) in sarcoidosis, silicosis and asbestosis. In: "Sarcoidosis and Other Granulomatous Disorders" (eds. W Jones Williams, BH Davies), Alpha Omega Publishing Ltd, Cardiff 1980, pp. 266-272 (107). Increased ACE activity was not specific for sarcoidosis patients as increased activity was seen in silicosis and asbestosis as well.

Selroos O, Tiitinen H, Grönhagen-Riska C, Fyhrqvist F, Klockars M. Angiotensin converting enzyme and lysozyme in sarcoidosis. In: "Sarcoidosis and Other Granulomatous Disorders" (eds. W Jones Williams, BH Davies), Alpha Omega Publishing Ltd, Cardiff 1980, pp. 303-310 (108). Increased serum ACE activity correlated positively with serum concentrations of lysozyme (96,101,103-105,107-108).

Oksanen V, Fyhrquist F, Grönhagen-Riska C, Somer H. CSF angiotensin-converting enzyme in neurosarcoidosis. Lancet 1985; 1(8436):1050-1051 (109).

Oksanen V., Grönhagen-Riska C, Tikanoja S, Somer H, Fyhrquist F. Cerebrospinal fluid lysozyme and β_2-microglobulin in neurosarcoidosis. J Neurol Sci 1986; 73:79-87 (110). Angiotensin converting enzyme, lysozyme and β_2-microglobulin were measured and found pathologically increased in cerebrospinal fluid in patients with neurosarcoidosis. The results will be mentioned in the section on neurosarcoidosis.

Grönhagen-Riska C, Fyhrqvist F, Välimäki M, Lamberg B-A. Thyroid hormones affect serum angiotensin I converting enzyme levels. Acta med scand 1985; 217:259-264 (111). The authors reported that thyroid hormon affects the activity in serum of ACE. The use of systemic ACE inhibitors may lower the assay of ACE .

Grönhagen-Riska C, Koivisto V, Riska H, von Willebrand E, Fyhrqvist F. ACE in physiologic and pathologic conditions. In: "Sarcoidosis and Other Granulomatous Disorders (eds. C Grassi, G Rizzato, E Pozzi), Elsevier Science Publ, Amsterdam 1988, pp 203-212 (112). The variation in serum ACE in physiological and pathological conditions has been thoroughly reviewed by Grönhagen-Riska et al.

Beta$_2$-microglobulin

β_2-microglobulin is a low molecular weight protein associated with histocompatibility (HLA) antigens. Activated lymhocytes release increased amounts of β_2-microglobulin. The assay has been used to monitor lymphoma patients.

Selroos O. Value of biochemical markers in serum for determination of disease activity in sarcoidosis. Sarcoidosis 1984; 1:45-49 (113).

Selroos O, Klockars M. Relation between clinical stage of sarcoidosis and serum values of angiotensin converting enzyme and beta$_2$-microglobulin. Sarcoidosis 1986; 4:13-17 (114).

Selroos O. Biochemical markers in sarcoidosis. CRC Critical Reviews in Clinical Laboratory Sciences 1986; 24:185-216 (115).

Selroos and Klockars evaluated the use of β_2-microglobulin in monitoring patients with sarcoidosis. They found that β_2-microglobulin was predominantly increased in patients with acute sarcoidosis and in patients with progressive relapsing disease. In the acute sarcoidosis patients β_2-microglobulin usually was normalized within one to three months. In long lasting stable disease state β_2-microglobulin was usually normal. The results indicated that β_2-microglobulin was a marker of early lymphocyte activation in sarcoidosis.

Adenosine deaminase

Klockars M, Pettersson T, Selroos O, Weber T. Activity of serum adenosine deaminase in sarcoidosis. Clin Chem 1984; 31:155 (116).

Klockars M, Pettersson T, Weber TH, Fröseth B, Selroos O. Angiotensin-converting enzyme, lysozyme, beta-2-microglobulin and adenosine deaminase in sarcoidosis. Arch Monaldi 1984; 39:345-356 (117). Adenosine deaminase (ADA) is essential for differentiation of lymphoid cells, particularly of T-lymphocytes. As a marker of lymphocyte activity Klockars et al determined ADA activity in 18 sarcoidosis patients with acute disease and in additional eight with erythema nodosum and acute disease, 14 with chronic disease and six with a chronic relapsing disease, and finally in nine patients with a chronic inactive sarcoidosis. ACE activity and β_2-microglobulin were simultaneously measured. ADA was abnormally increased only in sarcoidosis patients with chronic active relapsing disease. Compared with β_2-microglobulin determination of ADA was of limited value.

Soluble interleukin 2 receptor

Selroos O, Pietinalho A, Fröseth B. Biochemical markers in sarcoidosis with special reference to soluble interleukin-2 receptor in serum. Sarcoidosis 1992; 9,suppl.1:435-436 (118). Selroos et al measured soluble interleukin 2 receptor (IL-2R) and IL-2 in 83 sarcoidosis patients and 28 healthy subjects. In sarcoidosis patients with active disease a close positive correlation was found between IL-2R and ACE, lysozyme and β_2-microglobulin. In longitudinal studies, IL-2R and β_2-microglobulin followed each other very closely indicating that these two markers measured the lymphocytic activation in sarcoidosis.

Procollagen III-N-terminal peptide (PIIINP)

Tukiainen P, Risteli J, Salonen E-M, Laitinen T, Taskinen E. Procollagen-III-N-terminal (P-III-NP) and I-C-terminal (PICP) peptides are not markers of fibrosis in sarcoidosis. Sarcoidosis 1994; 11:84 (119). Bronchoalveolar lavage was performed in 40 patients with sarcoidosis and in 15 healthy control subjects or patients with chronic bronchitis. Procollagen-III-N-terminal peptide (P-III-NP) and procollagen-I-C-terminal (PICP) were measured. The patients with sarcoidosis who did not heal completely after an observation period of 36±10 months (n=18) had the same P-III-NP content (3.9±6.7 μg/mL) as the healed patients (n=22; 2.3±4.0 μg/mL). The patients treated because of far advanced parenchymal disease (n=14) had higher P-III-NP content (5.3±7.1 μg/mL) than the patients without treatment (n=26) (1.8±3.7 μg/mL; $p<0.05$). PICP was slightly but not significantly increased among non-healed patients (n=14; 1.7±2.1 μg/mL) compared to the healed patients (n=20; 0.7±0.5 μg/mL; $p<0.07$). Patients on treatment with corticosteroids had higher PICP values (n=8; 2.1±2.3 μg/mL) than untreated

patients (n=26; 0.8±0.6 μg/mL; p<0.03). A positive correlation was found between the peptid values and the protein content and lymphocyte count in BAL fluid. It appeared that P-III-NP and PICP values in BAL fluid are not markers of fibrosis but evidently related to inflammation.

Selroos O, Pietinalho A, Fröseth B. Serum procollagen III N-terminal peptide levels in sarcoidosis. Sarcoidosis 1994; 11:84 (120). Serum concentrations of procollagen-III-N-terminal peptide (P-III-NP) weres measured in 83 sarcoidosis patients and 22 healthy control subjects. The sarcoidosis patients had a significantly increased mean concentration (3.6±1.6 μg/mL; mean±SD) compared with controls (2.8±0.6; p<0.001). A positive correlation between P-III-NP and serum β_2-microglobulin was found (r=0.40; p<0.001). No difference in P-III-NP values was seen between patients with clinically active and less active disease as determined by serum ACE, β_2-microglobulin and the clinical picture. Untreated patients with active disease had higher P-III-NP values (4.2±1.5 μg/mL) than untreated patients with less active disease (3.0±1.0 μg/mL; p<0.02). Patients on treatment with corticosteroids exhibited large variations in P-III-NP values. Patients who deteriorated during a 3-year follow-up had initially higher mean values (3.9±1.0 μg/mL) compared with patients showing a spontaneous resolution (2.9±0.7 μg/mL). Repeated measurements of P-III-NP in 39 patients showed variations in parallel with serum β_2-microglobulin and interleukin receptor (IL-2R) levels, but not with serum ACE, lysozyme or hyaluronan.

Circulating immune complexes

Selroos O, Klockars M, Kekomäki R, Penttinen K, Lindström P, Wager O. Circulating immune complexes in sarcoidosis. J Clin Lab Immunol 1980; 3:129-132 (121). Selroos et al studied circulating immune complexes (CIC) with five different methods (3 platelet tests, a solid phase swine C1qB-ELISA test, a KgB-ELISA) using 112 sera from 33 sarcoidosis patients: 12 with acute disease (known duration of sarcoidosis <3 months), eight with subacute disease (duration 6 month to 2 years) and 13 with chronic sarcoidosis (duration >5 years). CIC were detected in all patients at some time of follow-up with different techniques. All patients with acute sarcoidosis had CIC in the first serum samples drawn.

Rheumatoid factor (RF) was also measured using an IgM-RF-ELISA. RF was positive (SD>3) in 19 of the first bleedings from the 33 patients with sarcoidosis (57%) and in 19 of 50 sera from blood donors (38%). The corresponding percentages of positivity (titres >16) in the RF-latex test were 9% and 10% respectively. Thus neither of the two RF tests gave significantly different percentage of positivity between sarcoidosis patients and controls.

Rheumatoid factor

Selroos O, Klockars M. Rheumatoid factor in sarcoidosis. In: "Proceedings of the 3rd European conference on sarcoidosis and other granulomatous disorders 1980" (ed. B Djuric), Sremska Kamenica, Novi Sad, 1982 pp. 126-129 (122). Selroos and Klockars investigated the presence of an IgM-rheumatoid factor (IgM-RF) in 112 sera from 33 sarcoidosis patients with acute, subacute or chronic sarcoidosis using a RF-ELISA method. Serum ACE and lysozyme were measured at the same time. RF was found in the first bleeding in 83% of patients with acute sarcoidosis, in 63% of patients with subacute disease, and in 31% of patients with chronic sarcoidosis. A significant correlation was found between RF and elevated ACE and/or lysozyme values. During a 3-year follow-up RF activity disappeared in most patients whose sarcoidosis became inactive.

Combinations of markers of disease activity

In several studies in sarcoidosis patients with different stages of disease serum angiotensin converting enzyme (ACE), lysozyme, β_2-microglobulin, IL-2R and procollagen-III-N-terminal peptide (P-III-NP) have been used in parallell over time (96,101,103-110,113,115,117,118,120,122). The overrall conclusion of these studies was that in acute and relapsing sarcoidosis the markers measuring lymphocytic activity (β_2-microglobulin and IL-2R) are increased. As granulomas develop (activation of the monocyte-macrophage-epithelioid cell line) ACE and lysozyme increase. At the same time the activity of the lymphocytic markers decreased. ACE and lysozyme can

be said to measure the total amount of granulomas in the body.
Biochemical markers in serum, such as ACE, lysozyme and β_2-microglobulin are valuable indicating disease activity. Their diagnostic usefulness is however poor but serial determinations of all of them give a good picture of development of the clinical disease. However, the decision to start, continue or discontinue therapy with corticosteroids must still depend on the clinical evaluation, symptoms, chest radiographs and lung function tests.

Martinez-Bravo M-J, Wahlund CJE, Qazi, KR, Moulder R, Lukic A, Rådmark O, Lahesmaa R, Grunewald J, Eklund A, Gabrielsson S. Pulmonary sarcoidosis is associated with exosomal vitamin D–binding protein and inflammatory molecules. J Allergy Clin Immunol 2017; 139:1186–1194 (123). The authors aimed to provide an understanding of the proinflammatory role of bronchoalveolar lavage fluid (BALF) exosomes in patients with sarcoidosis and to find candidates for disease biomarkers. They performed a mass spectrometric proteomics characterization of BALF exosomes from 15 patients with sarcoidosis and 5 healthy control subjects and verified the most interesting results with flow cytometry, ELISA, and Western blot analyses in an additional 39 patients and 22 control subjects.More than 690 proteins were identified in the BALF exosomes, several of which displayed significant upregulation in patients, including inflammation-associated proteins, such as leukotriene A_4 hydrolase. Most of the complement-activating factors were upregulated, whereas the complement regulator CD55 was seen less in patients compared with healthy control subjects. In addition, for the first time, they detected vitamin D–binding protein in BALF exosomes, which was more abundant in patients. To evaluate exosome-associated vitamin D–binding protein as a biomarker for sarcoidosis, they investigated plasma exosomes from 23 patients and 11 healthy control subjects and found significantly higher expression in patients. Together, these data contributed to understanding the role of exosomes in lung disease and provided suggestions for highly warranted sarcoidosis biomarkers. Furthermore, the validation of an exosome-associated biomarker in the blood of patients provides novel, and less invasive, opportunities for disease diagnosis.

Genetic studies

The frequency of familiar sarcoidosis in Finland is higher than in the reference population (18,36). This was confirmed in a Finnish and Danish population-based cohort study with 210 twin pairs.

Sverrild A, Backer V, Kyvik KO, Kaprio J, Milman N, Svendsen CB, Thomsen SF. Heredity in sarcoidosis: a registry-based twin study. Thorax 2008; 63:894-896 (124). Compared with the general population there was an 80-fold increased risk of developing sarcoidosis in co-twins of affected monozygotic brothers or sisters. The increased risk in dizygotic twins was only 7-fold. Aetiological model fitting gave a heritability of sarcoidosis of 0.66 (95% CI 0.45 to 0.80).

There is a polymorphism in the ACE gene. This polymorphism has also been studied in Finnish sarcoidosis series.

Pietinalho A, Furuya K, Yamaguchi E, Kawakami Y, Selroos O. The angiotensin-converting enzyme DD gene is associated with poor prognosis in Finnish sarcoidosis patients. Eur Respir J 1999; 13:723-726 (125).

Lahtela LE, Wennerström A, Pietinalho A, Petrek M, Lokki M-L, Selroos O. ACE gene variants in a Finnish sarcoidosis population. Sarcoidosis Vasc Diffuse Lung Dis 2017; 34:104-114 (126).

In the first small study it seemed that patints who were homozygots for the DD gene (deletion) more often had a chronic disease with less favourbale prognosis compared with patients with the insertion (II) or ID genotypes (125). However, this finding could not be replicated in a later and much larger study (126). In this latter study the authors wanted to extend the knowledge of the role of the ACE gene, not just insertion/deletion (I/D) polymorphism, in a Finnish sarcoidosis population. They genotyped 29 single nucleotide polymorphisms (SNPs) spanning from the 5' upstream to the 3' downstream region of the ACE gene from 188 sarcoidosis patients (resolved disease, n=90; persistent disease, n=98) and from 150 controls. These SNPs included tag SNP rs4343 for I/D polymorphism. No association was detected be-

tween I/D genotypes and disease susceptibility or prognosis. They found a novel SNP (rs9905945) in the 5'upstream region of the ACE gene to be moderately associated with favourable disease prognosis (p=0.035, OR=2.034 (95%CI 1.045-3.960)). However, in a replication study including 139 Czech sarcoidosis patients (resolved disease, n=47; persistent disease, n=92) and 176 healthy controls the SNP rs9905945 did not show any association with prognosis of sarcoidosis. The study further characterized genetic differences between Finnish sarcoidosis patients with different prognosis and population-specific genotype distribution. Nevertheless it seemed that variants in the ACE gene do not considerably influence the course of disease in Finnish sarcoidosis patients.

A series of further *genetic sarcoidosis studies* were carried out at the HLA laboratory at the Haartman-institute in Helsinki (Head: Marja-Liisa Lokki).

Wennerström A, Pietinalho A, Vauhkonen H, Lahtela L, Hedman J, Purokivi M, Varkki E, Seppänen M, Lokki M-L, Selroos O. HLA-DRB1 allele frequencies and C4 copy number variation in Finnish sarcoidosis patients and associations with disease prognosis. Human immunology 2012; 73:93-100 (127). Three genes were studied in the major histocompatibility complex region (HLA-DRB1 and complement C4A and C4B) in patients with resolved disease after a 2-year follow-up (n=90) and in patients whose disease was still active at that time point (n=98) and compared them with controls (n=150). The primary aim was to detect genetic differences between the patient groups. The study showed that the susceptibility allele for sarcoidosis was HLA-DRB1*15:01 (p=0.011; odds ratio [OR]=1.67) and the protective allele was HLA-DRB1*01:01 (p=0.001; OR=0.43). HLA-DRB1*03:01 was associated with resolving disease when compared with the persistent group (p=0.011; OR=2.22). The probability of having resolving disease was even greater if the patient had HLA-DRB1*03:01 and did not have extrapulmonary lesions (p=0.001; OR=3.39). By evaluating amino acid variants of the HLA-DRB1 gene, the authors found that specific amino acids in pockets 4, 7, and 9 were associated with the prognosis of sarcoidosis. The results supported the importance of HLA-DRB1 as a predisposing gene for sarcoidosis. Particularly, HLA-DRB1*03:01 and polymorphisms of DRB1 pocket residues were associated with a favorable prognosis. Thus, accurate categorization of disease phenotype and HLA-DRB1 sequencing offer a basis for disease course estimation of sarcoidosis.

Wennerström A, Pietinalho A, Lasota J, Salli K, Surakka I, Seppänen M, Selroos O, Lokki ML. Major histocompatibility complex class II and BTNL2 associations in sarcoidosis. Eur Respir J 2013; 42:550-553 (128). The study showed that resolved and persistent sarcoidosis have different combinations of disease-related MHC markers (*HLA-DRB1*, *-DPB1* and *BTNL2* rs2076530). Therefore, the importance of accurate phenotypic categorisation of sarcoidosis patients was highlighted and underlined the necessity of studying wider regions of the MHC in order to investigate independent risk factors.

Lahtela EL, Wolin A, Anttila V, Grunewald J, van Moorsel CHM, Petrek M, Eklund A, Grutters J, Kolek V, Padyukov L, Pietinalho A, Ronninger M, Seppänen M, Selroos O, Lokki M-L, Mrazek F. SNP variants in MHC are associated with sarcoidosis susceptibility – a joint analysis of four European populations. Front Immunolog 2017. Apr 19;8:422. doi: 10.3389/fimmu.2017.00422.eCollection 2017 (129). Four genes in the MHC Class III region (*LTA, TNF, AGER, BTNL2*) and *HLA-DRA* with tag-SNPs and their relation to *HLA-DRB1* alleles were studied to detect variants predisposing to sarcoidosis and to identify differences between patient subgroups. Results from a joint analysis of four study populations (Finnish, Swedish, Dutch, and Czech) were presented. Patients with sarcoidosis (*n*=805) were further subdivided based on the disease activity and the presence of Löfgren's syndrome. In a joint analysis, seven SNPs were associated with non-Löfgren sarcoidosis (NL; the strongest association with rs3177928, *P*=1.79E–07, OR=1.9) and eight with Löfgren's syndrome [Löfgren syndrome (LS); the strongest association with rs3129843, *P*=3.44E–12, OR=3.4] when compared with healthy controls (*n*=870). Five SNPs were associated with sarcoidosis disease course (the strongest association with rs3177928, *P*=0.003, OR=1.9). The high linkage disequi-librium (LD) between SNPs

and an *HLA-DRB1* challenged the result interpretation. When the SNPs and *HLA-DRB1* alleles were analyzed together, independent association was observed for four SNPs in the *HLA-DRA/BTNL2* region: rs3135365 (NL; *P*=0.015), rs3177928 (NL; *P* <0.001), rs6937545 (LS; *P*=0.012), and rs5007259 (disease activity; *P*=0.002). These SNPs act as expression quantitative trait loci (eQTL) for *HLA-DRB1* and/or *HLA-DRB5*. In conclusion, the authors found novel SNPs in *BTNL2* and *HLA-DRA* regions associating with sarcoidosis. The finding further established that polymorphisms in the *HLA-DRA* and *BTNL2* have a role in sarcoidosis susceptibility. This multi-population study demonstrated that at least a part of these associations are *HLA-DRB1* independent (e.g., not due to LD) and shared across ancestral origins. The variants that were independent of *HLA-DRB1* associations acted as eQTL for *HLA-DRB1* and/or *-DRB5*, suggesting a role in regulating gene expression.

Lahtela E, Wolin A, Pietinalho A, Lokki M-L, Selroos O. Disease marker combination enhances patient characterization in the Finnish sarcoidosis patients. Respir Med 2017; 132:92-94 (130). The authors discovered that a combination of the *ACE* SNP rs9905945 and previously reported HLA markers enhance the accuracy for predicting disease course in Finnish sarcoidosis patients further characterizing genetic differences between Finnish sarcoidosis patients with different prognosis. However, probable population specific distribution of the disease associated SNPs must be considered before its potential application to other populations.

In these studies HLA genes and haplotypes were investigated in patients with sarcoidosis cured within 2 years, or chronic cases with a duration of active disease for more than 5 years (126-130). The studies showed that sarcoidosis patients with the HLA type HLA-DRB1*03:01 and with the haplotype HLA-DRB1*04:01-DPB1*04:01 had a good prognosis. A novel SNP (rs9905945) was also found in the 5'upstream region of the ACE gene. Combination of this SNP with favourable HLA types enhanced the accuracy of prognosis estimation.

Tuberculin skin test

Patients with sarcoidosis may be tuberculin skin test negative even if they earlier have responded normally to skin testing. An exception is patients with acute sarcoidosis and erythema nodosum. They may have a normal tuberculin skin test reactivity (12,13).

Selroos studied the tuberculin sensitivity in 140 sarcoidosis patients by using 1 and 10 tuberculin units (TU) of purified protein derivate (PPD RT-23) (12). Of 36 patients with radiographic stage I disease and erythema nodosum (Löfgren's syndrome) 11 (30%) were positive to 1 TU, 15 (42%) to 10 TU and 10 (28%) remained negative to 10 TU. In 41 patients with stage I disease without erythema nodosum the corresponding percentages were 27%, 32% and 41%. In 55 patients with stage II the figures were 18% 1 TU positive, 27% 10 TU positive, and 55% 10 TU negative. Of 8 patients with stage III disease 6 were 10 TU negative. In the control series the lowest frequency of 1 TU positive subjects (55%) was seen in the age group 20-29 years compared to 29% in the sarcoidosis group. In the age group 40-49 years a positive reaction to 1 TU was noticed in 79% of the subjects compared with 26% among the sarcoidosis patients. Thus, as a group, patients with sarcoidosis had a depressed tuberculin skin test sensitivity compared with healthy controls.

Hannuksela M, Salo OP. The significance of the quantitative Mantoux test in sarcoidosis. Scand J Resp Dis 1969; 50:259-264 (131). Hannuksela and Salo evaluated the significance of quantitative Mantoux tests in 283 patients with sarcoidosis. Despite a significant weakening of tuberculin sensitivity in sarcoidosis patients compared with controls, a positive reaction to 1 tuberculin unit (TU) of purified tuberculin derivative (PPD) or even to 0.1 TU of PPD did not exclude sarcoidosis. On the other hand, a positive reaction to 0.01 TU or less did not occur in any stage of sarcoidosis. Tuberculin sensitivity also seemed to be independent of Kveim test reactivity. Patients with erythema nodosum were in general more tuberculin sensitive than those with other forms of sarcoidosis.

Selroos O, Niemistö M. Tuberculin sensitivity in active and cured sarcoidosis in Finland. In: Pro-

ceedings of the VI International Conference on Sarcoidosis, (eds. K Iwai, Y Hosoda), University of Tokyo Press, 1974 pp 248-252 (132). Selroos and Niemistö reported on tuberculin skin test sensitivity in 115 patients who had been tuberculin tested during the active disease state and later on when sarcoidosis was cured. They found that among 32 patients with stage I or stage II disease and erythema nodosum 20 patients (63%) were more sensitive at the cured state. Among 48 patients without erythema nodosum 28 patients (37%) were more sensitive in the cured state.

Elo, in a series of 353 sarcoidosis patients found 18.1% to be positive to 1 TU, 4.8% negative to 1 TU, 28.3% positive to 10 TU, 15.9% negative to 10 TU, 13.1% positive to 100 TU, and 19.8% negative to 100 TU (18).

By using a dialyzable transfer factor Horsmanheimo and Virolainen were able to induce tuberculin skin sensitivity in skin negative sarcoidosis patients (133-135).

Horsmanheimo M. In vitro induced tuberculin sensitivity in sarcoid patients with a negative skin test to 100 TU. In: Proceedings of the VI International Conference on Sarcoidosis, (eds. K Iwai, Y Hosoda), University of Tokyo Press, 1974; 182-185 (133). The effect of the lymphocyte transforming factor (LTF) on tuberculin-negative cord blood and sarcoid lymphocytes was studied. Non-sensitive sarcoid lymphocytes responded to LTF as well as non-sensitive control lymphocytes. Sensitive sarcoid lymphocytes produced significantly less active LTF than did control lymphocytes. The results suggested that the impairement of delayed hypersensitivity in sarcoidosis is not caused by a primary response defect of the lymphocytes, but may be caused by a defect in, or lack of, some mediators of delayed hypersensitivity.

Horsmanheimo M, Virolainen M. Acquisition of tuberculin sensitivity after injection of dialyzable transfer factor in sarcoidosis. Ann N Y Acad Sci. 1976;278:129-135 (134).

Horsmanheimo M, Virolainen M. Transfer of tuberculin sensitivity by transfer factor in sarcoidosis. Clin Immunol Immunopathol. 1976; 6(2):231-237 (135)**.** This report described the acquisition of tuberculin shin-test sensitivity by six of eight sarcoid patients after a single injection of dialyzable transfer factor (TFd) from tuberculin-positive healthy subjects. The acquisition of cellular immunity to purified protein derivative (PPD) by the recipient was also demonstrated in vitro by PPD-induced blast transformation. TFd did not cause PPD-induced blast transformation when added directly to cultures of lymphocytes from sarcoid patients.

Patients with defective cellular immunity as measured by tuberculin skin test reactivity were tested in another study by Horsmanheimo et al.:
Horsmanheimo M, Virolainen M, Nikoskelainen J, Fudenberg HH. Lymphoblastoid cell lines from sarcoid patients. Clin Immunol Immunopathol. 1978; 9:419-424 (136). The relation between skin test reactivity, the prevalence and titers of antibodies to Epstein-Barr virus capsid antigens (VCA), and the frequency with which lymphoblastoid cell lines could be established was studied in 28 patients with sarcoidosis. The geometric mean titer of anti-VCA antibodies was significantly higher in patients with sarcoidosis. The ability to establish lymphoblastoid cell lines, known to be associated with Epstein-Barr virus, was significantly higher for sarcoid patients, especially chronic sarcoid patients.

Kveim-Siltzbach skin test

As mentioned above Putkonen was an early investigator of the Kveim skin test (3-7,48). He used lymph node material from patients with sarcoidosis. He did not use the test so much as a diagnostic tool, but was more interested in the nature and mechanisms behind the reaction. Later work in Putkonen's department brought further light on this skin reaction.

Rechardt L, Mustakallio KK. Macrophage response to epidermal abrasion in sarcoidosis. Its relation to the patient' s Kveim reactivity. Acta pathol microbial scand 1965; 65:521-527 (137). Rechardt and Mustakallio described a macrophage response to epidermal abrasion in sarcoidosis and its relation to the patient' s Kveim reactivity with the skin window technique in 20 Kveim-tested sarcoidosis patients and in 20 healthy, sex and age matched control subjects. Within the six initial hours of inflamma-

tion, induced by epidermal abrasion, the number of macrophages emigrating onto the skin window coverslips in active sarcoidosis was two- to sixfold the number seen in stationary cases or in healthy subjects. A significant correlation was found between the relative macrophage count and the rapidity with which the Kveim papule attained the diameter of 5 mm. Injection of Alcian blue two weeks before the skin window examination afforded evidence for the histiocytic nature of a part of the emigrated macrophages. The hyperactive macrophage response to epidermal abrasion in sarcoidosis appeard to reflect the activity of the disease.

Mustakallio KK, Hannuksela M. Fate of Kveim material in skin. "Fifth International Conference on Sarcoidosis, Prague 1969" (eds. L Levinský, F Macholda), Universita Karlova Praha 1971, pp. 382-383 (138). Mustakallio and Hannuksela described the fate of Kveim test material by using injections of Alcian blue. The Kveim material could be traced by using test material precipitated and stained with Alcian blue. The blue material was found within some epithelioid-cell-like cells, possibly derived from blood-borne macrophages.

Salo OP, Hannuksela M. Immunohistology of the Kveim reaction. Ann Clin Res 1972; 4:169-172 (139). The immunohistology of the Kveim reaction was described by Salo and Hannuksela. Twenty sarcoidosis patients with positive Kveim reactions were studied immunohistologically for the presence of immunoglobulins, complement and fibrin. In 19 cases IgM was found in the vessel walls inside the Kveim granulomas. Complement was bound in vivo in the same places as IgM. A fibrillary network of material antigenically identical with fibrin formed a part of the ground substance of the granuloma.

Hannuksela M, Salo OP, Karvonen J. Immunohistological development of the Kveim reaction. Dermatologica. 1975; 151:354-358 (140). Hannuksela et al studied the immunohistology of the Kveim reaction by taking biopsies of test sites at various intervals after injection of the test material. Immunoglobulins were present in half of the cases after 2-7 days. After two weeks 50% of the biopsies showed immunoglobulins. After longer duration 79% of the biopsies showed immunoglobulins. Out of 52 specimens examined with specific conjugates, IgM was found in 42, and IgG and IgA in one case each. Complement C3 was found in 83% of 47 examined biopsies. Immunoglobulins and complement were always seen in vessel walls, never elsewhere in the tissues.

Klockars and Selroos reported on the occurrence of lysozyme within the Kveim skin test papule (95).

Finally, Horsmanheimo et al studied blast cell transformation *in vitro* by adding Kveim test material to cell cultures of sarcoidosis patients:
Horsmanheimo M. Lymphocyte transformation and the Kveim test. Lancet 1973; 1(7812):1120-1121 (141).

Horsmanheimo M. Phytohaemagglutinin-, tuberculin- and Kveim-induced blast transformation in sarcoidosis. In: Proceedings of the VI International Conference on Sarcoidosis, (eds. K Iwai, Y Hosoda), University of Tokyo Press, 1974;177-181 (142). Horsmanheimo could not detect any cell transformation when adding Kveim material to the cultures, irrespective of what type of Kveim material she used.

Horsmanheimo M, Horsmanheimo A, Fudenberg HH, Siltzbach LE, McKee KT. Leukocyte migration agarose test (LMAT) in sarcoidosis using Kveim test material. Br J Dermatol. 1978; 99:263-270 (143).

Horsmanheimo M, Horsmanheimo A, Fudenberg HH, Siltzbach LE, KcKee KT. Kveim test reactivity with leukocyte migration in agarose and lymphocyte transformation tests. In: Sarcoidosis and Other Granulomatous Diseases (eds, W Jones Williams, DH Davies), Alpha Omega Publ Ltd, Cardiff 1980 pp. 186-190 (144). Similarly, Horsmanheimo et al used a two-stage leukocyte migration agarose test (indirect LMAT) - a sensitive assay in vitro for cell-mediated immunity – to study Kveim reactivity in patients with sarcoidosis. No Kveim-induced inhibition of leukocyte migration in agarose was found. The results suggested that the Kveim reaction was not an expression of cell-mediated immunity.

Selroos O. Sarkoidos och mb. Crohn – etiologisk spekulation (Sarcoidosis and Mb Crohn – specu-

lation on aetiology). Nord Med 1971; 85:50-51 (in Swedish) (145). Selroos discussed possible aetiological links between sarcoidosis and Mb Crohn.

Hannuksela M, Alkio H, Selroos O. Kveim reaction in Crohn's disease. Lancet 1971;II:974 (146). Kveim tests were performed in patients with Mb Crohn and found negative in all 16 patients tested.

Mycoplasma skin test

Horsmanheimo M, Jansson E, Hannuksela M, Fudenberg HH. Studies in sarcoidosis: intradermal Mycoplasma test. Am Rev Respir Dis. 1978; 117:975-979 (147). In a further *in vitro* study Horsmanheimo et al studied skin test effects of Mycoplasma strain 215-M, closely related to Mycoplasma orale type 1, grown in human macrophage monolayers. Sonicated homogenates of macrophages diluted in saline solution were used for intradermal skin tests in 19 patients with sarcoidosis and in 25 patients with a variety of other diseases. Positive skin-test reactions to this newly developed Mycoplasma test material were observed significantly more often in the patients with sarcoidosis than in the other patients.

In vitro lymphocyte transformation tests

In vitro lymphocyte transformation tests with the addition of Kveim test material to cell cultures have been mentioned above.

Selroos O. In vitro cultured lymphocytes in sarcoidosis. Rapports du symposium européen de la sarcoidose (ed.Y Gallopin), Masson et Cie, Paris, 1967, pp 275-279 (148). In a pilot study Selroos cultured lymphocytes of sarcoidosis patients and controls in vitro. By adding phytohaemagglutinin to the culture the cells went into mitosis and the percentage of transformed cells could be estimated. This was before the technique with labelled thymidine incorporation was established. He could not find an increased lymphocyte transformation compared with controls by adding tuberculin or Kveim test material. However, in a mixed lymphocyte culture with cells from two sarcoidosis patients an enhanced spontaneous lymphocyte transformation was seen.

Later on Horsmanheimo et al reported large series of lymphocyte transformation tests, some of them summarized in her academic thesis (15).

Horsmanheimo M, Virolainen M. Enhancement of tuberculin-induced lymphocyte transformation by precultivated macrophages from patients with sarcoidosis. Scand J Immunol. 1974; 3(1):21-27 (149). The authors precultivated autologous macrophages and found that they enhanced the early PPD-induced blastogenic response of tuberculin-sensitive lymphocytes. This effect was not caused by a diffusible macrophage product. Macropbages exposed to PPD and subsequently washed caused as high a response as did PPD in cultures without precultivated macrophages. Sensitive macrophages were not able to induce nonsensitiv-lymphocytes to respond to PPD. Precultivated macrophages from tuberculin-negative patients with sarcoidosis enhanced the PPD-induced transformation of sensitive lymphocytes, as did autologous macrophages. Cord blood-derived macrophages were significantly less effective.

Horsmanheimo M, Virolainen M. Correlation of phytohaemagglutinin-induced lymphocyte transformation with clinical manifestations of sarcoidosis. Acta Pathol Microbiol Scand B Microbiol Immunol. 1974; 82:122-126 (150). The authors studied the *in vitro* lymphocyte activation by phytohaemagglutinin (PHA) using tritiated thymidine (^{3}H-TdR) incorporation in the buffy coat cell cultures of 90 sarcoidosis patients. The response did not differ from that of control subjects. However, when the series was divided into clinical subgroups they found that the PHA induced response was significantly higher in patients with erythema nodosum than in those sarcoidosis patients without erythema nodosum.

Horsmanheimo M. Correlation of tuberculin-induced lymphocyte transformation with skin test reactivity and with clinical manifestations of sarcoidosis. Cell Immunol 1974; 10:329-337 (151). Horsmanheimo also studied *in vitro* lymphocyte reactivity to tuberculin (PPD) in buffy coat cultures from 87 patients with sarcoidosis and from 64 controls. A strong correlation was found etween PPD-induced lymphocyte transformation and skin reactivity. No signiIicant differences were found in the *in*

vitro response of lymphocytes from skin test positive patients with sarcoidosis and from controls with the same degree of skin test reactivity. In patients with sarcoidosis negative to 100 TU, tuberculin sensitivity could be demonstrated *in vitro* significantly more often than in comparison subjects. Both *in vivo* and *in vitro* tuberculin sensitivity and "spontaneous" transformation were significantly more frequent in patients with erythema nodosum.

Horsmanheimo M. Lymphocyte transforming factor in sarcoidosis. Cell Immunol. 1974; 10:338-343 (152). In a further study Horsmanheimo induced lymphocyte transforming factor (LTF) by tuberculin in cultures of lymphocytes from tuberculin-sensitive healthy subjects. In the presence of tuberculin, lymphocytes from nonsensitive patients with sarcoidosis responded to LTF as did cord blood lymphocytes. The LTF activity correlated with the tuberculin skin sensitivity of the healthy adult donors. Less LTF activity was produced by lymphocytes from tuberculin-sensitive patients with sarcoidosis than by those from the tuberculin-sensitive controls.

Development of cellular immunity during follow-up

Selroos O, Nikinmaa B, Koivunen E, Riska H, Tiitinen H, Weber T. Cellular immunity during follow-up of patients with sarcoidosis of varying duration. Clin exp Immunol 1982; 50: 25-33 (153). Selroos et al followed the cellular immunity during one year in 43 sarcoidosis patients divided into those with acute sarcoidosis (duration of symptoms less than 2 months; n=12), subacute sarcoidosis (symptoms for 6-12 months; n=20), and chronic sarcoidosis (symptoms for more than 2 years). These patients were studied at study entry and at 3-month intervals during one year. The following tests were performed at each visit: total number of peripheral blood lymphocytes, T- and B-cell lymphocyte counts, *in vitro* leukocyte migration inhibition test with PPD, BCG and Kveim test material, and *in vitro* lymphocyte activation tests using phytohaemagglutinin (PHA), concanavalin A (Con A), PPD and pokeweed mitogen (PWM). Serum ACE activity was also measured. Twelve healthy subjects formed a control group. At the start of the study the most abnormal findings were seen in the group of patients with acute sarcoidosis, followed by those with subacute disease. The most significant changes during follow-up were also seen in acute sarcoidosis. The smallest changes were found in the patients with chronic disease. However, it was noticed that great inter-individual variations occurred. The leukocyte migration inhibition test the migration index in the tests with PPD was higher (i.e. migration was less inhibited) in all groups compared with controls. In patients with increased ACE activity the migration index was significantly higher than in patients with normal ACE activity. Differences in ACE activity did not influence the *in vitro* activation of lymphocytes.

Grönhagen-Riska C, Fyhrqvist F, Pettersson T, Welin MG, Weber TH. Leukocyte migration inhibiting effect of purified human lung angiotensin I-converting enzyme. In: Sarcoidosis and Other Granulomatous Disorders (eds. J Chrétien, J Marsac, JC Saltiel), Pergamon Press, Paris 1983 pp 326-331 (154). Grönhagen-Riska et al. performed leukocyte migration inhibition tests with purified human lung ACE. ACE caused about 50% migration inhibition compared with controls. The cell response was dose dependent. After separation of mononuclear cells from granulocytes, ACE did not cause significant migration inhibition of neutrophils. Migration inhibition of leukocytes was not affected by a specific ACE inhibitor, Captopril®. These results suggested that ACE contributes to immunological phenomena as seen in e.g. sarcoidosis.

Serological tests

Puolakkainen M, Campbell LA, Kuo CC, Leinonen M, Grönhagen-Riska C, Saikku P. Serological response to Chlamydia Pneumoniæ in patients with sarcoidosis. J Infect 1996; 33:199-205 (155). The antigen-specific serological response to Chlamydia pneumoniae was studied in 24 patients with sarcoidosis and compared to that seen in acute C. pneumoniae respiratory infection. By the micro-immunofluorescence test, five sarcoidosis patients had acute antibody, 15 had chronic antibody and four had no antibody against C. pneumoniae. By enzyme immunoassay, 20 sarcoidosis patients had antibody against ReLPS but that cross-reacted with

chlamydial LPS. Immunoblot analysis of sera using purified C. pneumoniae elementary bodies showed that recognition of the 40 kDa C. pneumoniae major outer membrane protein was rare (20%). Reactivities with proteins with Mw of 42 K (70%), 60 K (65%), 98 K (55%) and 52 K (50%) were often noted. To study reactivity of chlamydial HSP 60 in sarcoidosis sera, sarkosyl-soluble (contains the 60 kDa HSP) and sarkosyl-insoluble (contains the 60 kDa structural protein) fractions of C. pneumoniae elementary bodies were prepared. The 60 kDa structural protein was recognized with equal frequency by sera from patients with sarcoidosis and acute respiratory infection, while the HSP 60 was more frequently recognized by sera with acute respiratory infection than sarcoidosis. Recombinant fusion proteins expressed from pGEX-2T containing overlapping DNA fragments of the C. pneumoniae 60 kDa HSP gene were purified. Different recognition patterns were identified for sera from sarcoidosis patients and from patients with acute C. pneumoniae respiratory infection.

Extrapulmonary sarcoidosis

Ocular sarcoidosis

Sarcoidosis may affect the eyes. Uveitis is the most common manifestation but many other lesions may occur including glaucoma and optic nerve inflammation. In many hospitals ophthalmological consultation belongs to the routine examinations in patients with known or suspected sarcoidosis. In Finland Anni Karma has been the leading lady in the field of sarcoidosis and the eyes.

Selroos in 1969 in is his thesis reported eye manifestations in 10% of 140 patients, (20% in those examined by an ophthalmologist) (12), Elo in 1977 in 3.7% of 158 patients with extrapulmonary sarcoidosis (18), and Pietinalho in 2000 in 7% of 571 patients (21).

A 10-year retrospective survey on 653 cases of uveitis was published from Northern Finland (32). Among these patients nine (1.4%) were verified as having sarcoidosis. Karma found this figure too low (33). In her prospective study of patients with suspected or known sarcoidosis she found a frequency of 28% among 281 patients (16).

Leino M, Tuovinen E, Romppanen T. Orbital sarcoidosis. A case report. Acta ophthalmol 1982; 60:809-814 (156). A case of ophthalmic sarcoidosis with systemic sarcoid involvement was presented. The case presented a large firm tumour of the right orbit with only minor ocular involvement. The diagnosis was based on histological verification at various sites.

Karma A, Sutinen S. Conjunctival biopsy in sarcoidosis. Acta Ophthalmol Suppl. 1975; 125:52-54 (157).

Karma A, Sutinen S, Huhti E. Sidekalvobiopsia sarkoidoosissa (Conjunctival biopsy in sarcoidosis). Duodecim 1983; 99:869-876 (in Finnish) (158). Karma published on conjunctival biopsies. In the first study on 70 patients with sarcoidosis conjunctival biopsies showed granulomas in 11 casaes (16%) (157). In her later series of 230 patients with 218 biopsies (60 with active sarcoidosis, 158 with inactive disease) she found 21 biopsies in the active group compatible with sarcoidosis (35%) and in 16 (10%) of those with inactive disease (16). In 66 patients, biomicroscopy of the conjunctivae revealed nodules with an appearance suggestive of sarcoidosis. In 27 cases (41%) epithelioid cell granulomas were found. No granulomas were seen in 40 control subjects.

Karma A, Sutinen S, Karma P. Conjunctival and tonsillar biopsies in sarcoidosis. Chest. 1980; 78:900-901 (159). Simultaneous conjunctival and tonsillar biopsies were obtained in a series of 139 patients with sarcoidosis, 40 having an active disease. Conjunctival biopsies were taken from the lower fornix of 138 patients. The biopsies revealed granulomas in 23 patients (17%). Of the 35 patients with conjunctival nodules suggestive of sarcoidosis on slip-lamp examination 14 (40%) showed granulomas on biopsy. Granulomas were found more frequently in patients with active disease (13/44) compared with 10/92 in those with inactive disease. Granulomas were also more often found in patients with other extrapulmonarry manifestations (17/69) than in patients with only intrathoracic lesions (6/67). Tonsil-

lar biopsies revealed granulomas in five out of 50 patients (10%), all with active disease (5/17).

Karma A. Sarcoidosis of the lacrimal sac. Arch Ophthalmol. 1982; 100:664 (160). Karma also reported on sarcoidosis of the lacrimal sac and or lacrimal duct in five patients in a series of 281 patients. These five patients were all elderly women with a florid course of disease. Biopsy of the lacrimal gland was performed in three caes and granulomas were found in two cases.

Karma A. Diagnosing sarcoidosis by transconjunctival biopsy of the lacrimal gland. Am J Ophthalmol. 1984; 98:640-642 (161). In another study Karma discussed transconjunctival biopsies of the lacrimal gland. For safety reasons she did not recommend biopsies of the lacrimal gland but noticed that among her 281 patients with verified sarcoidosis 32 (13%) had a decreasd lacrimal secretion in the Shirmer I test. Of these patients 22 had permanently decreased secretion.

Karma A, Poukkula A, Ruokonen A. Gallium67 citrate scanning in patients with lacrimal gland and conjunctival sarcoidosis. A report on three cases. Acta Ophthalmol (Copenh). 1984; 62:549-555 (162).

Karma A, Poukkula AA, Ruokonen AO. Assessment of activity of ocular sarcoidosis by gallium scanning. Br J Ophthalmol. 1987; 71:361-367 (163). Karma et al reported on the use of ^{67}gallium scintigraphy in patients with conjunctival and/or lacrimal sarcoidosis. The first study was a report on three patients and demonstrated the sensitivity of the procedure (162). Two patients had a progressive pulmonary sarcoidosis of recent onset and in one patient, with a chronic course of the disease, the lung changes had resolved. All three patients had a conjunctival sarcoid change confirmed by biopsy and a lacrimal gland affection suggested by clinical examination. A highly increased ^{67}Gallium citrate uptake in the lacrimal and parotid glands as well as in the nasopharynx was found in all patients, and an increased lung uptake was found in the newly detected cases. It was concluded that gallium scanning is a sensitive method for detecting minute ophthalmic changes in sarcoidosis. It also reveals chronic localized ocular affection in cases in which the lung changes are no longer detectable. In addition to uptake in the lacrimal gland and parotis, minute conjunctival lesions could also be detected. In the second study ^{67}Gallium citrate uptake over the orbits, parotid glands, and lungs was examined in six newly detected patients with sarcoidosis and 17 with chronic sarcoidosis (163). Six of 23 (26%) had uveitis, 18/23 (78%) decreased lacrimal secretion, and 13/16 (81%) epithelioid cell granulomas in conjunctival biopsies. Ten patients with other diseases served as controls. Only five patients had ocular complaints and two had enlarged parotid glands. ^{67}Ga uptake over the orbits and parotids was measured by a quantitative computer based method. Gallium uptake was significantly higher over the orbits ($p < 0.001$) and parotids ($p < 0.01$) in the newly detected patients and in the parotids ($p < 0.01$) in the chronic group than the corresponding uptake in the controls. Gallium scan was a good method for revealing even symptomless ophthalmic sarcoid changes. However, in chronic sarcoidosis an equal or only slightly increased gallium uptake over the orbits compared with background activity does not exclude ocular sarcoid disease.

Karma A, Laatikainen L. Fluorescin iris angiography in nodular sarcoid iritis. Int Ophthalmol 1981; 3:97-106 (164). Karma et al also studied the value of fluorescein iris angiography in the diagnosis and follow-up of ocular sarcoidosis. Iris angiography was studied in five patients with nodular iritis and histologically verified generalized sarcoidosis. On the angiograms the sarcoid nodules appeared as hyperfluorescent patches which always exceeded the number of nodules seen by biomicroscopy. Fresh iris nodules were characterized by mild diffuse fluorescence and dilatation and leakage of the adjacent vessels whereas old granulomas were covered by tortuous neovascular vessels which in the active stage of the disease leaked fluorescein profusely. After recovery or between recurrent attacks the amount of leakage decreased or stopped although the neovascular network did not disappear. At recurrences new areas of fluorescence due to fresh nodules were observed in addition to intense leakage from some of the previous lesions. Most of the small nodules were situated in the pupillary part of the iris resulting in dilatation and abnormal permeability of all the peripupillary vessels. The weakness of absence or diffuse leakage from the

radial vessels of the iris agreed with the proliferative nature of sarcoid nodular iritis and explained the low-grade symptoms of the patients.

Karma A, Huhti E, Poukkula A. Course and outcome of ocular sarcoidosis. Am J Ophthalmol. 1988; 106:467-472 (165).

Karma A. Longitudinal study of ocular sarcoidosis. In: "Sarcoidosis and Other Granulomatous Disorders" (eds C Grassi, G Rizzato, E Pozzi) Elsevier Science Publ, Amsterdam 1988, pp 511-513 (166). The course and outcome of patients with ocular sarcoidosis were reported in two studies. In a series of 281 patients with histologically confirmed sarcoidosis, 79 initially had ophthalmic sarcoid manifestations. Of 22 patients with uveitis, 21 were seen regularly as long as the inflammation was active, and 71 of the 79 patients (90%) underwent a follow-up study five to 16 years (mean, nine years) later and using the same protocol. In the 21 patients with uveitis, the disease exhibited either a monophasic course (eight patients) with favorable visual outcome or a relapsing course (13 patients) with severe visual loss in five eyes. Thirty-three patients showed chronic ophthalmic changes at the follow-up examination, including conjunctival granulomas (13 patients), lacrimal gland involvement (22 patients), uveitis (four patients), and involvement of lacrimal passages (three patients). In 15 of these 33 patients, the general physical examination and the chest radiograph showed no evidence of systemic sarcoidosis. However, the serum angiotensin converting enzyme level was increased in a significantly greater proportion of these 15 patients than in the patients assessed as totally recovered from sarcoidosis.

Karma A, Mustonen A. Optic nerve involvement in sarcoidosis. Neuro-ophthalmology 1985; 5:231-246 (167). Six patients with generalized histologically confirmed sarcoidosis developed optic nerve involvement, two at the onset and four during the chronic course of the disease. Two patients had granulomas of the prelaminar part of the optic nerve, two had optic disc oedema with an unusual appearance, one had retrobulbar optic neuritis, and one has glaucomatous cupping of the optic nerve head. Four patients had no visual complaints at the time optic nerve abnormality was detected.

Karma A. Ophthalmologic peculiarities in sarcoidsosis. Klin Minbl Augenheilkd 1987; 191:253-259 (168). This paper delt with the frequency of different ophthalmic changes in sarcoidosis patients and their morphological and photographical characteristics. In addition, the diagnostic value of conjunctival biopsy was evaluated. The findings were based on repeated ophthalmological examinations of an unselected group of 281 patients with histologically confirmed sarcoidosis. Conjunctival (37/218) and lacrimal gland (33/254) changes were encountered more often than sarcoid uveitis (22/281), and a conjunctival granuloma was the most frequent single sarcoid ophthalmic finding. Sarcoid changes in the eyes and the adnexae were often characterized by a scarcity of symptoms and a typical outward appearance. In some cases of sarcoid uveitis fluorescein angiography revealed in the iris and the retina nodules which showed features suggesting the proliferative nature of the disease. The iris infrared transillumination technique illustrated the affinity of sarcoid nodules in the pupillary area. Conjunctival biopsy showed epithelioid cell granulomas compatible with sarcoidosis in nearly half of the patients in whom it was suspected in a slit-lamp examination of the conjunctivae. In the diagnosis of sarcoidosis, conjunctival biopsy is a procedure to be recommended before more demanding methods are tried.

Karma A, Taskinen E, Kainulainen H, Partanen M. Phenotypes of conjunctival inflammatory cells in sarcoidosis. Br J Ophthalmol 1992; 76:101-106 (169). Karma et al also studied the phenotypes of the infiltrating mononuclear cells of the lower fornix conjunctiva of nine patients with sarcoidosis and six controls using monoclonal antibodies and a modified immunoperoxidase method. Four patients had sarcoidosis of recent onset (duration of 2 years or less) and five patients had a chronic disease (duration of 3 or more years). The inflammatory cells in the sarcoid conjunctival specimens were predominantly T lymphocytes, the vast majority of which were of T helper/inducer subtype expressing Leu-3a + 3b positivity. The ratio of T helper/inducer cells to T suppressor/cytotoxic cells was 3.9 on average but only 0.9 in controls. Epithelioid cell granulomas were seen in three specimens in one case of recent onset and in two chronic cases comprising a marked amount (more than 15 cells/visual field) of cells bearing phenotypes

of macrophages, T cells, T helper/inducer cells and HLA-DR antigen, and in smaller quantities of T suppressor/cytotoxic cells. The mean number of all immunocompetent cell subtypes of specimens from newly diagnosed patients exceeded that of specimens from chronic patients. The authors believed that the sarcoid immune reaction in the conjunctiva is a dynamic process in which proliferation of immunocompetent mononuclear cells precedes the stage of granuloma formation.

Karma A. Diagnostic aspects of ocular sarcoidosis. Sarcoidosis 1994; 11:58-60 (170)**.**

Finally Karma summarized her experiences as an ophthalmologist interested in sarcoidosis in her summary publication on diagnosis of ocular sarcoidosis.

Kotaniemi K, Aho K, Kotaniemi A. Uveitis as a cause of visual loss in arthritides and comparable conditions. J Rheumatol 2001; 28:309-312 (171)**.** The authors described uveitis as a cause of visual loss in patients with various diseases, including sarcoidosis. In a retrospective study on 174 patients with uveitis and visual handicap they found five patients (3%) with sarcoidosis.

Al-Jamal RT, Kivelä T. Progressive visual loss and an optic disc tumour in a young man. Acta Ophthalmol 2008; 86:341-343 (172). A 27-year-old, previously healthy man experienced a painless decrease in vision in his right eye for 1 week, associated with floaters. He had also experienced bilateral irritation of his eyes 3 months previously, which he thought had been caused by conjunctivitis. An optic disc granuloma with venous congestion and small haemorrhages was noticed in the right eye. The vitreous was hazy and visual field examination showed a central scotoma. Three monhs later his vision deteriorated, bilateral pulmonary infiltrates and mediastinal lymphnodes were found. Serum ACE was increased. He was then treated with corticosteroids.

As mentioned earlier, Immonen et al studied the use of angiotensin-converting enzyme determinations in lacrimal granulomas (99) and in conjunctival granulomas (100).

Neurosarcoidosis

If Anni Karma was the Finnish expert in ocular sarcoidosis, Virpi Oksanen had the same position regarding neurosarcoidosis. However, the first publication/review in Finland on CNS sarcoidosis was that by Hokkanen et al in 1977.

Hokkanen E, Hakkarainen H, Hannuksela M. Aivoston sarkoidoosi (CNS sarcoidosis). Duodecim 1977; 93:199-205 (in Finnish) (173).

The publications by Oksanen et al delt with various clinical pictures and manifestations of neurosarcoidosis, with measurements of activity markers in cerebrospinal fluid and imaging of central nervous system (CNS) lesions (174-183).

Oksanen V, Grönhagen-Riska C, Fyhrquist F, Somer H. Systemic manifestations and enzyme studies in sarcoidosis with neurologic involvement. Acta med scand 1985; 218:123-127 (174). In an early retrospective study Oksanen et al evaluated the dissemination and activity of systemic disease in 50 patients with neurosarcoidosis, 24 of whom presenting with neurologic symptoms. During follow-up, five patients never developed detectable systemic disease. In 26 patients, sarcoidosis had previously been diagnosed, but in 11 (42%) of them the neurologic symptoms were initially not connected with this disease. During follow-up, extraneural features were those of sarcoidosis in general. However, 23 patients (46%) had normal chest radiograph on admission to neurologic examinations. Fourteen (35%) of 40 examined patients had ocular changes, 13 (33%) of 39 hypercalciuria and 13 (26%) of 50 skin manifestations. Serum angiotensin converting enzyme (ACE) was elevated in only 31% of the patients. Measureable amounts of ACE were recorded in the cerebrospinal fluid from 13 of 17 examined patients. During follow-up the activity of neurosarcoidosis seemed to be linked to the course of systemic disease in general. Together with Fyhrquist et al Oksanen reported on the new assey of measuring angiotensin converting enzyme activity in cerebrospinal fluid, CSF (109).

Oksanen V, Fyhrqvist F, Grönhagen-Riska C, Somer H. CSF angiotensin-converting enzyme in neurosarcoidosis. Lancet 1985; I:1050-1051 (109).

The initial clinical usefulness of the method in patients with neurosarcoidosis was reviewed in a series of seven patients. The ACE activity in CSF followed the clinical course of disease. Persistently high activity was associated with poor prognosis.

Oksanen V, Grönhagen-Riska C, Tikanoja S, Somer H, Fyhrquist F. Cerebrospinal fluid lysozyme and β_2-microglobulin in neurosarcoidosis. J Neurol Sci 1986; 73:79-87 (110). Later on Oksanen published on the usefulness of cerebrospinal fluid lysozyme (CSF) and β_2-microglobulin in neurosarcoidosis. Lysozyme and β_2-microglobulin were measured in serum and CSF in 32 sarcoidosis patients. Twenty opf them had neurosarcoidosis. CSF lysosome was elevated in 15 of 20 patients with neurosarcoidosis but only in four of 12 with extraneural disease. CSF β_2-microglobulin values were elevated in 13 of 19 and in one of 11 patients, respectively. Both CSF lysozyme and β_2-microglobulin were useful in the follow-up of neurosarcoidosis.

Oksanen V. Neurosarcoidosis: clinical presentations and course in 50 patients. Acta neurol scand 1986; 73:283-290 (175). The clinical presentations and course in 50 patients with neurosarcoidosis was presented. Sarcoidosis presented first with neurological signs in 24 patients (48%), but systemic symptoms developed later in all but five patients. Main neurologic involvements were central nervous system lesions in 33 patients (66%), cranial nerve paresis in 12 (24%), and peripheral nerve lesions on five patients (10%). Seventeen patients (34%) had more then one type of neurologic involvement. Routine CSF parameters showed unspecific abnormalities in 35 patients. CSF angiotensin converting enzyme activirty was elevated in 18 of 31 patients (58%). Brain computerized tomography was abnormal in 13 of 32 patients (41%). Visual and brainstem evoked potentials were abnormal in ten (43%) and eight (35%) of 23 patients, respectively, suggesting subclinical lesions in 13 patients. Neurologic signs improved in 24 patients (48%), remained stable in 11 (22%), and progressed in 15 patients (30%). Cranial nerve lesions improved most often. The effect of treatment with corticosteroids was inconsistent.

Oksanen V, Salmi T. Visual and auditory evoked potentials in the early diagnosis and follow-up of neurosarcoidosis. Acta neurol scand 1986; 74:38-42 (176). Visual and brainstem auditory evoked patentials (VEPs, BAEPs) were recorded in 23 patients with neurosarcoidosis and the results were reported. Eight patients (35%) had abnormal BAEPs and 10 (43%) abnormal VEPs. Four of the eight patients with abnormal BAEPs had facial paresis, one had impaired memory and only three had symptoms and signs compatible with brainstem lesions. Seven of the patients with abnormal VEPs had no visual symptoms. The findings suggested that BAEP and VEP can reveal subclinical nervous nsystem involvement in sarcoidosis and can help in early diagnosis. Successive recordings in five patients showed that BAEP and VEP were useful in the follow-up.

Ketonen L, Oksanen V, Kuuliala I, Somer H. Hypodense white matter lesions in computed tomography in neurosarcoidosis. J Comput Assist Tomograph 1986; 10:181-183 (177). Cerebral computed tomography (CT) was performed on 32 patients with neurosarcoidosis and found to be abnormal in 13 (41%). One of the most common abnormalities (five patients) was represented by low density white matter lesions. Other types of lesions were ventricular enlargement and mass lesions. Nineteen of the 32 patients had normal CT findings. Nine magnetic resonance imaging examinations (MRI) carried out in seven patients failed to reveal more lesions than CT.

Ketonen L, Oksanen V, Kuuliala I. Preliminary experience of magnetic resonance imaging in neurosarcoidosis. Neuroradiology 1987; 29:127-129 (178). In another study 12 MR scans performed on seven patients with neurosarcoidosis were presented. The most common abnormalities were ventricular enlargement (four patients) and diffuse periventricular white matter changes (three patients). Infarcts were seen in three patients and mass lesion in one. The lesions were seen in both T1 and T2 weighted images. The results were compared with CT findings. MRI seemed to be more sensitive than CT in detecting white matter changes and infarcts. Ventricular enlargement and granulomas were equally well seen with both modalities.

Oksanen V. New cerebrospinal fluid, neurophysiological and neuroradiological examinations in

the diagnosis and follow-up of neurosarcoidosis. Sarcoidosis 1987; 4:105-110 (179), and

Oksanen V. Comparison of new CSF, neurophysiological and neuroradiological studies in sarcoidosis. In: "Sarcoidosis and Other Granulomatous Disorders (eds. C Grassi, G Rizzato, E Pozzi), Elsevier Science Publ, Amsterdam 1988, pp. 381-382 (180). Oksanen summarized her experiences of neurosarcoidosis in two publications dealing with activity markers in cerebrospinal fluid (CSF), neurophysiological and neuroradiological examinations in the diagnosis and follow-up of neurosarcoidosis. She concluded that for a compete evaluation of a patient with suspected neurosarcoidosis, combination of the newer CSF activity markers, neurophysiological, and neuroradiological studies is needed. CSF enzyme studies are useful in cerebral lesions and especially in cranial nerve lesions where CT and MRI usually fail to show abnormalities. Evoked potential examinations are helpful noninvasive methods for detection of both cerebral and cranial nerve lesions. Although CT and MRI are mainly normal in patients with cerebral symptoms they can disclose unexpected CNS involvement even in patients with mainly cranial nerve affection. Nevertheless, histologically verified systemic sarcoidosis still remains the mainstay of diagnosis.

Bode MK, Tikkakoski T, Tuisku S, Kronqvist E, Tuominen H. Isolated neurosarcoidosis – MR findings and pathologic correlation, Acta radiol 2001; 117:132-142 (181). A 49-year-old woman with isolated neurosarcoidosis was presented. The main symptom was loss of vision in the left eye. Brain MR imaging showed 6 high-signal white matter lesions frontotemporally on proton density and T2-weighted turbo spin-echo images. Coronal fat-saturated turbo FLAIR images of the orbits showed a swollen left optic nerve with increased signal intensity, which finding had not been previously published in sarcoid optic neuropathy. A control MR examination showed meningeal enhancement of the left optic nerve and leptomeningeal enhancing lesions around the brain stem. Spinal MR revealed leptomeningeal enhancement throughout the spinal cord and asymptomatic enhancing cauda equina lesions, mimicking subarachnoid tumour seeding, and an enhancing nerve root mass at Th12/L1. Biopsy of the latter lesion revealed non-caseating granulomas consistent with sarcoidosis.

Tuisku IS, Konttinen YT, Soinila S, Karma A, Tervo TM. Neurosarcoidosis mimicking Sjögren's syndrome. Acta Ophthalmol Scand 2004; 82:599-602 (182). Tuisku et al published a case report dealing with a patient with sarcoidosis mimicking Sjögren's syndrome. A 58-year-old man with sick sinus syndrome and bradycardia, which was treated with a pacemaker, developed first right and then left facial palsy. Subsequently, multiple cranial nerve palsies developed and later spontaneously resolved. Neurosarcoidosis was suspected at that stage, but excluded because the patient had no typical sarcoid lung changes, his serum and cerebrospinal fluid angiotensin converting enzyme activity levels were normal and a computed tomography scan disclosed no central nervous system changes. During follow-up, the patient developed extremely dry eyes and mouth, suggesting Sjögren's syndrome. Rheumatology consultation did not reveal any autoimmune or visceral features typical of Sjögren's syndrome and autoantibodies were negative. However, both labial salivary gland and conjunctival biopsies revealed non-caseating granulomas, and neurosarcoidosis was diagnosed.

Martikainen MH, Grönroos JO, Vuorinen T. Detection of human herpesvirus 7 DNA from the CSF in association with neurosarcoidosis. J Med Virol 2013; 85:1935-1939 (183). Martikainen et al detected human herpes virus 7 DNA from the CSF in association with neurosarcoidosis. This study reported a previously healthy, immunocompetent adult male in whom human herpesvirus 7 (HHV-7) DNA was detected continuously from the cerebrospinal fluid (CSF). This patient developed definite sarcoidosis with primary symptomatic manifestations in the central nervous system (CNS). The initial presentation was with loss of visual acuity and papilloedema. Brain MR imaging at presentation confirmed papilloedema, but otherwise there were no focal abnormalities or signs of hydrocephalus. CSF investigation revealed pleocytosis and elevated protein levels. HHV-7 DNA was detected repeatedly from CSF but not from blood over one year follow-up. High resolution computed tomography of lungs was normal. Positron emission tomography showed several metabolically active lymph nodes in the me-

diastinum, and the histopathological investigation revealed granulomatous inflammation consistent with sarcoidosis. The finding of HHV-7 DNA in the CSF in the context of neurosarcoidosis had not been reported previously. The detection of HHV-7 DNA may have resulted from the selective activation of CD4+ T-lymphocytes in the CSF caused by neurosarcoidosis.

Cardiac sarcoidosis

The first Finnish report on possible cardiac involvement in sarcoidosis was published in 1972 and described ECG abnormalities in patients with diagnosed sarcoidosis (184). Possible cardiac lesions were not histologically verified.

Selroos O. Myocardial sarcoidosis. Scand J Respir Dis 1972; 53:349-366 (184).

Elo reported ECG changes in five of 158 patients with sarcoidosis (14), and Pietinalho in two patients of 571 (17).

Uusimaa P, Ylitalo K, Anttonen O, Kerola T, Virtanen V, Pääkkö E, Raatikainen P. Ventricular tachyarrhythmia as a primary presentation of sarcoidosis. Europace. 2008; 10:760-766 (185). Ventricular tachyarrhythmias as a primary presentation of sarcoidosis were described. In nine patients sarcoidosis was manifested as ventricular tachycardia (VT). The age of the patients was from 33 to 68 years. Sarcoidosis was diagnosed by endomyocardial biopsy in eight patients and by lymph node biopsy in one patient. The presenting arrhythmia varied from non-sustained VT to incessant VT and ventricular fibrillation. All patients received implantable cardioverter defibrillator (ICD) and anti-arrhythmic medication. High-dose steroid treatment was used in eight cases. During the follow-up (50±34 months), five patients underwent appropriate ICD therapies and non-sustained VT episodes were detected in four patients. Two patients developed incessant VT, which was treated by catheter ablation. One patient was referred for heart transplantation.

Kandolin became interested in sarcoidosis and presented her doctoral thesis on cardiac sarcoidosis in 2015 (19). Together with a number of co-investigators she published papers dealing with sarcoidosis and the heart (186, 188-194).

Kandolin R, Lehtonen J, Schildt J, Granér M, Salmenkivi K, Ahonen A, Karhumäki L, Kupari M. Cardiac sarcoidosis (Sarcoidoisis of the heart). Duodecim.2009; 125:2344-2350 (in Finnish) (186). The first publication described 44 hospitalized patients with cardiac sarcoidosis. In 24 cases the diagnosis had been verified by myocardial biopsy (six of these patients had sarcoidosis outside the heart). Twenty patients had biopsy-verified sarcoidosis with cardiac manifestations. The age distribution was similar in the two groups: 50 (range 34-66) and 49 (range 26-75) years, respectively. There were 19 and 11 women, five and nine men in the groups. The symptoms were as follows (% of patients): complete heart block 58 and 50, ventricular tachycardia 67 and 60, ventricular fibrillation 13 and 10, and heart failure (ejection fraction <55%) 83 and 30 %, respectively. Electrocardiograms (% of patients) showed right bundle branch block (RBBB) in 33 and 40, left BBB in 42 and 5, and normal ECG in 17 and 25 %, respectively. Serum ACE was increased (% of patients) in 14 and 44, serum lysozyme in 44 and 64, and serum calcium in 4 and 11 %, respectively. Fifty and 42 % of the patients got a pacemaker; 50 and 25% anti-arrhythmic pacemakers. One fourth of the patients in each group were treated with immunosuppressive drugs in addition to corticosteroids. Twenty-nine patients in the first group underwent cardiac transplantation. Cardiac ultra sound examination revealed septum abnormalities in 63 and 50% of the patients. During follow-up on third of the patients experienced life-threatening events. Forty-two and 35% of the patients died due to cardiac problems.

Kokki T, Sipilä HT, Teräs M, Noponen T, Durand-Schaefer N, Klén R, Knuuti J. Dual gated PET/CT imaging of small targets of the heart: method description and testing with a dynamic heart phantom. J Nucl Cardiol 2010 ;17:71-84 (187). The aim was to develop and evaluate a dual gating method for improving the detection of small targets of the heart. The method utilized two independent triggers which were sent periodically into list mode data based on respiratory and ECG cycles. An algorithm for generating dual gated segments from list mode data was developed. Patient study of suspected cardiac sar-

coidosis showed sharper spatial myocardial uptake profile and improved detection of small myocardial structures such as papillary muscles. The dual gating method improves detection of small moving targets in a phantom and it is feasible in clinical situations.

Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. Circ Arrhythm Electrophysiol 2011; 4:303-309 (188). Kandolin et al used the pacemaker (PM) registry of Helsinki University Central Hospital to identify all patients aged 18 to 55 years who underwent PM implantation for atrio-ventricular blocks (AVB) between January 1999 and April 2009 and reviewed their medical records. In total, 133 patients had either second- or third-degree AVB as an indication for PM. Of them, 61 had a known cause for AVB, and they were excluded from further analyses. Among the remaining 72 patients with initially unexplained AVB, biopsy-verified cardiac sarcoidosis (CS) or giant cell myocarditis (GCM) were found in 14 (19%) and 4 (6%) patients, respectively. The majority (16/18, 89%) were women. Among adult patients aged <55 years, the prevalence of CS and GCM combined was 14% (95% CI, 7.7% to 19.3%) of the whole AVB population and 25% (95% CI, 15% to 35%) of those with an initially unexplained AVB. Over an average of 48 months of follow-up, seven (39%) of 18 patients with CS or GCM versus one of the 54 patients in whom AVB remained idiopathic, experienced either cardiac death, cardiac transplantation, ventricular fibrillation, or treated sustained ventricular tachycardia ($p<0.001$). The authors concluded that CS and GCM explain ≥25% of initially unexplained AVB in young and middle-aged adults. These patients are at high risk for adverse cardiac events.

Kandolin R, Lehtonen J, Graner M, Schildt J, Salmenkivi K, Kivistö SM, Kupari M. Diagnosing isolated cardiac sarcoidosis. J Intern Med 2011; 270:461-468 (189).

In a further retrospective study Kandolin et al reviewed the medical records, laboratory test results, imaging studies and pathological analyses of 74 patients with either histologically proven or clinically probable cardiac sarcoidosis (CS) in the years 2000 to 2010. Fifty-two patients had histologically proven CS, of whom 33 (26 women) had disease that was clinically isolated to the heart. Sarcoidosis was detected in the first endomyocardial biopsy (EMB) in 10 of the 31 patients who underwent biopsy. CS was found by repeated EMBs, targeted by cardiac maging, in seven additional patients, and 11 patients were diagnosed by sampling 18-F-fluorodeoxyglucose position emission tomography-positive mediastinal lymph nodes at mediastinoscopy. Together, the first biopsy (cardiac or mediastinal lymph node) provided the diagnosis in 34%, the second biopsy in 31% and the third in 22% of biopsied patients with isolated CS. Four (13%) of the remaining diagnosis were made after cardiac transplantation and one in a patient who did not undergo biopsy, at autopsy after sudden cardiac death. The authors concluded that cardiac sarcoidosis may present without clinically apparent disease in other organs. At least two-thirds of patients remain undiagnosed after a single EMB session. The detection rate can be improved by repeated and imaging-guided cardiac or mediastinal lymph-node biopsies. Nevertheless, false-negative biopsy results remain a problem in CS patients with no apparent extracardiac disease.

Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Ylitalo K, Kaikkonen K, Tuohinen S, Haataja P, Kerola T, Kokkonen J, Pelkonen M, Pietilä-Effati P, Utriainen S, Kupari M. Cardiac Sarcoidosis: Epidemiology, Characteristics and Outcome over 25 Years in a Nationwide Study. Circulation 2015; 131:624-632 (34). Kandolin et al performed a study to asess the epidemiology, characteristics, and outcome of cardiac sarcoidosis (CS) in Finland. They identified in retrospect all adult patients (>18 years of age) diagnosed with histologically confirmed CS in Finland between 1988 and 2012. A total of 110 patients (71 women), 51±9 years of age (mean±SD), were found and followed up for outcome events to the end of 2013. The annual detection rate of CS increased >20-fold during the 25-year period, reaching 0.31 in 1×10^5 adults between 2008 and 2012. The 2012 prevalence of CS was 2.2 in 1×10^5. Nearly two thirds of patients had clinically isolated CS. Altogether, 102 of the 110 patients received immunosuppressive therapy, and 56 received an intracardiac defibrillator. Left ventricular function was impaired (ejection fraction <50%) in 65 patients

(59%) at diagnosis and showed no overall change over 12 months of steroid therapy. During follow-up (median, 6.6 years), 10 patients died of a cardiac cause, 11 patients underwent cardiac transplantation, and another 11 patients suffered an aborted sudden cardiac death. The Kaplan-Meier estimates for 1-, 5-, and 10-year transplantation-free cardiac survival were 97%, 90%, and 83%, respectively. Heart failure at presentation predicted poor outcome (log-rank P=0.0001) with a 10-year transplantation-free cardiac survival of only 53%. The authors concluded that the detection rate of CS has increased markedly in Finland over the last 25 years. With current therapy, the prognosis of CS appeared better than generally considered, but patients presenting with heart failure still had poor long-term outcome.

Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Kaikkonen K, Haataja P, Kerola T, Kupari M. Usefulness of cardiac troponins as markers of early treatment response in cardiac sarcoidosis. Am J Cardiol 2015; 116:960-964 (190). Kandolin et al studied measurements of high-sensitivity cardiac troponin T or troponin I (hs-cTnT/I) taken at presentation and during treatment in 62 patients with new-onset cardiac sartcoidosis (CS). There were 48 women; mean age 49 years. Hs-cTnT was measured in 50 patients and was elevated (>13 ng/L) at presentation in 26 of them (52%). Hs-cTnI was measured in the remaining 12 patients and was elevated (>0.04 ng/mL) in 7 of them (58%). Left ventricular ejection fraction averaged 43±14% in association with elevated hs-cTnT/I (n=33) versus 53±10% with normal hs-cTnT/I (n=29; p=0.001). Hs-cTnT/I was remeasured after 4 weeks of steroid therapy in 38 patients and was normalized in 16 of the 24 (67%) with an elevated pretreatment concentration and remained normal in the rest of the 14 patients (p <0.001). During follow-up (median, 17 months), cardiac death (n=2), aborted sudden death (n=5), sustained ventricular tachycardia (n=8), or new complete atrioventricular block (n=1) was recorded in 11 of 33 patients with elevated hs-cTnT/I versus in 5 of 29 with normal hs-cTnT/I (log-rank p=0.068). Two-year event-free Kaplan-Meier cardiac survival estimate (95% confidence interval) was 67% (48% to 81%) with elevated hs-cTnT/I versus 93% (76% to 99%) with normal hs-cTnT/I. In CS, circulating hs-cTnT/I may help clinicians evaluate disease activity and treatment response. Their prognostic value remains tentative.

Simonen P, Lehtonen J, Kandolin R, Schildt J, Marjasuo S, Miettinen H, Airaksinen J, Vihinen T, Tuohinen S, Haataja P, Kupari M. F-18-fluorodeoxyglucose positron emission tomography-guided sampling of mediastinal lymph nodes in the diagnosis of cardiac sarcoidosis. Am J Cardiol 2015; 116: 1581-1585 (191). Histologic proof of granulomatous inflammation is prerequisite for the diagnosis of cardiac sarcoidosis (CS). Because of the limited sensitivity of endomyocardial biopsy (EMB) in sarcoidosis, confirmation often has to be acquired from extracardiac biopsies. Simonen et al set out to review experience of F-18-fluorodeoxyglucose positron emission tomography (F-18-FDG PET) in guiding extracardiac tissue biopsies in suspected CS. Sixty-eight consecutive patients with proved CS who had undergone cardiac F-18-FDG PET with (n = 57) or without whole-body imaging as part of initial diagnostic evaluation were included. Their hospital charts, imaging studies, and diagnostic biopsies were reviewed in retrospect. Whole-body PET images showed extracardiac foci of abnormally high F-18-FDG uptake in 39 of 57 patients, of whom 38 had involvement of mediastinal lymph nodes (MLN). Parallel F-18-FDG uptake was found in other lymph nodes (n=10), lungs (n=9), liver (n=3), spleen (n=2), and thyroid gland (n=1). Adding the mediastinal findings at cardiac PET without whole-body imaging, abnormal F-18-FDG uptake in MLN was found in totally 43 of the 68 patients with CS (63%). Histology of systemic sarcoidosis was known at presentation of cardiac symptoms in 8 patients. Of the 60 patients with missing histology, 24 patients underwent mediastinoscopy for sampling of PET-positive MLN, most often after nondiagnostic EMB (n=20); microscopy revealed diagnostic noncaseating granulomatous inflammation in 24 of the 24 cases (sensitivity 100%). In the remaining 36 patients, sarcoidosis histology was confirmed by EMB (n=30), by biopsy of lungs (n=2) or peripheral lymph nodes (n=2), or at autopsy (n=1) or post-transplantation (n=1). The authors concluded that MLN accumulate F-18-FDG at PET in most patients with CS and provide a highly productive source for diagnostic biopsies either primarily or subsequent to nondiagnostic EMB.

Ekström K, Lehtonen J, Hänninen H, Kandolin R, Kivistö S, Kupari M. Magnetic resonance Imaging as a predictor of survival free of life-threatening arrhythmias and transplantation in cardiac sarcoidosis. J Am Heart Assoc 2016; May 2; 5(5). pii: e003040 (192). Ekström et al investigated whether cardiac magnetic resonance imaging helps to predict outcome in cardiac sarcoidosis. Their study involved 59 patients with cardiac sarcoidosis (38 female, mean age 46±10 years) seen since February 2004 and followed up after contrast-enhanced cardiac magnetic resonance imaging. The extent of myocardial late gadolinium enhancement (measured as percentage of left ventricular mass), the volumes and ejection fractions of the left and right ventricles, and the thickness of the basal interventricular septum were determined and analyzed for prognostic significance. By April 2015, 23 patients had reached the study end point, consisting of a composite of cardiac death (n=3), cardiac transplantation (n=1), and occurrence of life-threatening ventricular tachyarrhythmias (n=19; ventricular fibrillation in 5 and sustained ventricular tachycardia in 14 patients). In univariate analysis, myocardial extent of late gadolinium enhancement predicted event-free survival, as did scar-like thinning (<4 mm) of the basal interventricular septum and the ejection fraction of the right ventricle (P<0.05 for all). In multivariate Cox regression analysis, extent of late gadolinium enhancement was the only independent predictor of outcome events on cardiac magnetic resonance imaging, with a hazard ratio of 2.22 per tertile (95% CI 1.07-4.59). An extent of late gadolinium enhancement >22% (third tertile) had positive and negative predictive values for serious cardiac events of 75% and 76%, respectively. Findings on cardiac magnetic resonance imaging and the extent of myocardial late gadolinium enhancement was of particular help to predict serious cardiac events in cardiac sarcoidosis.

Simonen P, Lehtonen J, Gylling H, Kupari M. Cholesterol metabolism in cardiac sarcoidosis. Atherosclerosis 2016; 48:210-215 (193). Cardiac sarcoidosis (CS) was inactive or responding to treatment in all patients. Concentrations of serum, LDL, and HDL cholesterol and serum triglycerides were similar in CS patients and in control subjects. Cholesterol absorption markers were higher in CS patients than in controls (e.g. serum campesterol to cholesterol ratio in CS 246±18 vs in controls 190±8 10(2) x μmol/mmol of cholesterol, p=0.001). Cholesterol synthesis markers were lower in CS patients than in controls (e.g. serum lathosterol to cholesterol ratio in CS 102±8 vs in controls 195±5 10(2) x μmol/mmol of cholesterol, p=0.000). In CS patients, cholesterol absorption markers significantly correlated with plasma prohormone brain natriuretic peptide (proBNP), a marker of haemodynamic load. High cholesterol absorption efficiency, which is suggested to be atherogenic, characterized the metabolic profile of cholesterol in CS patients. The association between cholesterol absorption efficiency and plasma proBNP concentration, which suggests a link between inflammation, cholesterol homeostasis, and haemodynamic load, warrants further studies in order to confirm this finding and to reveal the underlying mechanisms.

Tuominen H, Haarala A, Tikkakoski A, Korkola P, Kähönen M, Nikus K, Sipilä K. 18F-FDG-PET in Finnish patients with clinical suspicion of cardiac sarcoidosis: Female sex and history of atrioventricular block increase the prevalence of positive PET findings. J Nucl Cardiol. 2017 Jun 5. doi: 10.1007/s12350-017-0940-x. [Epub ahead of print] (194). Fluorodeoxyglucose positron emission tomography (FDG-PET) is a non-invasive imaging modality that has been shown to be a feasible method to demonstrate myocardial inflammation. 137 patients suspected of having cardiac sarcoidosis (CS) had undergone a dedicated cardiac FDG-PET examination. These examinations were retrospectively analyzed. 33 and 12 of the 137 patients had abnormal left and right ventricular (LV and RV) FDG-uptake, respectively. Abnormal LV-uptake and RV-uptake were significantly associated with female sex and a history of advanced AV-block (p<0.05). Abnormal RV-uptake was also associated with ventricular tachycardia and atrial fibrillation (p<0.05). 56% of the 27 female patients with a history of AV-block had a pathological PET finding compared to only 6% of the 49 male patients without a history of AV-block. There were 17 female patients with history of both AV-block and ventricular tachycardia, 71% of them had abnormal PET finding. Abnormal FDG-PET findings were associated with female sex, AV-block, and arrhythmias in this clinical cohort.

Sipilä K, Tuominen H, Haarala A, Tikkakoski A, Kähönen M, Nikus K. Novel ECG parameters are strongly associated with inflammatory 18F-FDG PET findings in patients with suspected cardiac sarcoidosis. Int J Cardiol 2017;249:454-460 (195). A total of 133 patients underwent cardiac FDG PET examination. The left ventricular FDG uptake was categorized as either normal or pathological. Additionally, in-depth analyses of resting ECG were performed. Among other parameters, the presence of septal and inferolateral remodelling was assessed. These are novel ECG parameters related to local structural changes in the myocardium. In the ECG, septal and inferolateral remodelling, as well as widespread QRS fragmentation were significantly associated with pathological left ventricular FDG uptake even if adjusted for age, sex, body mass index, underlying cardiovascular disease and cardiac medication ($p<0.05$ for all). When all these ECG parameters were combined in a logistic regression model, only septal remodelling remained independently associated with abnormal left ventricular uptake ($p<0.05$). The findings show that novel ECG parameters septal and inferolateral remodelling, as well as diffuse QRS fragmentation, are strongly associated with pathological cardiac findings in FDG PET. Thus, the presence of these ECG findings may warrant the clinician to consider the possibility of cardiac sarcoidosis.

Liver involvement

A few abnormal liver enzyme tests (alkaline phosphatase) were reported in the larger clinical series of patients with sarcoidosis. Selroos measured serum alkaline phosphatase in 107 patients (12). Elevated values were seen in only three patients, who also had hypercalcaemia and hypercalciuria. Two had radiographic stage III pulmonary lesions. The patient with stage II lesions had splenomegaly and skin lesions as well. Also Elo (18) found elevated alkaline phosphatase values in three patients out of 214 (1.4%) and Pietinalho in 4.4% of 505 patients (21).

Lehmuskalli E, Hannuksela M, Halme H. Liver in sarcoidosis. Acta med scand 1977; 202:289-293. (196). Liver biopsies were performed in 121 patients with sarcoidosis. Granulomas were found in 29 patients (24%). Granulomas were more often seen in patients with pulmonary parenchymal changes compared with patients with bilateral hilar lymphadenopathy alone.

Spleen

Selroos O. Sarcoidosis of the spleen. Acta med scand 1976; 200:337-340 (69)**.** In a series of 77 sarcoidosis patients (53 women; mean age 36 years) spleen size was measured with radiography. Six patients had a moderately enlarged spleen with a length exceeding 16 cm. Only one of them had a palpable spleen. One patient had signs of hypersplenism. Of the six patients one had pulmonary radiographic stage I disease, four stage II and one stage III. All patients underwent fine-needle aspiration biopsy of the spleen. The results are reported in the chapter about biopsy procedures.

Koivunen E. Bone marrow and spleen findings in sarcoidosis, Sarcoidosis Vasc Diffuse Lung Dis 1998; 15:81-82 (197)**.** The author described a series of 990 patients with sarcoidosis. Nine patients (0.9%) had a palpable spleen. A total of 270 patients were examined with radiographic tomography of the spleen. The speel size was estimated according to a splenic index (=spleen surface area in an anterioposterior projection, cm^2/body surface area of the patient, m^2). The mean spleen size in patients (52.0 ± 16.4 cm^2/m^2) was greater than in 91 controll subjects (40.1 ± 11.2 cm^2/m^2) ($p<0.001$). A spleen was considered enlarged when the index was more than the mean of the control subjects plus 2 SD. Seventy of the 270 patients had splenomegaly (26%). Splenomegaly was more common among parients with a long duration of disease (>2 years; 38%) compared with those with a short duration of disease (≤2 years; 23%; $p<0.05$). Thirty-three % of the patients with other extra pulmonary manifestations of sarcoidosis had splenomegaly (six with a palpable spleen), which was more often than in those patients without known extra pulmonary lesions (15% ;$p<0.01$).

Results of fine-needle aspiration biopsies of the spleen have been presented earlier (68-72).

Siniluoto TM, Tikkakoski TA, Lähde ST, Päivänsalo MJ, Koivisto MJ. Ultrasound or CT in splenic diseases? Acta Radiol. 1994; 35:597-605 (198).To

compare the value of ultrasound (US) and computed tomography (CT) for the detection and analysis of splenic abnormalities, the authors reviewed the medical records and imaging findings of 93 patients with 93 proven textural lesions of the spleen, which were visualized by US and/or CT. US revealed the abnormality in 91 (97.8%) patients and CT in 74 (79.6%) patients. US was more sensitive than CT in the detection of malignant lesions, particularly splenic lymphoma, while US and CT were equally effective in benign lesions. In two patients, *one with sarcoidosis* and the other with an acute infarct, the lesion was visualized by CT but not by US. On CT, i.v. injection of contrast material improved both the sensitivity of the examination and the delineation of the abnormality. The echogenicity or the attenuation of the lesions did not usually allow differentiation between the various benign and malignant splenic lesions. US was recommended as the method of choice for splenic imaging.

Kidney disease with/without hypercalcaemia and serum calcium values

Kuhlbäck B, Nyberg W. Hyperkalcemi och njurskada vid sarkoidos (Hypercalcaemia and renal damage in sarcoidosis). Finska Läk-Sällsk Handl 1955; 98:181-185 (in Swedish) (4)**.** This early paper on sarcoidosis described a 21-year old woman who fell ill with fever, enlarged lacrimal and parotis glands. Ophthalmological examination revealed bilateral uveitis and dacryocystitis. A chest radiograph showed bilateral hilar lymphadenopathy. A biopsy of a parotic gland showed granulomas consistent with sarcoidosis. The eyes were treated with topical corticosteroids and scopolamine, the parotis glands with radiotherapy. There was a spontaneous regression of the chest radiographic findings. Fourteen months later the patient was hospitalized again with stomach pain, vomiting and headache. Hypercalcaemia was found. The bilateral uveitis was active again and the chest radiographic picture had progrediated. A moderate renal insufficiency was noted. Ther patient was treated for two months with corticosteroids and recovered completely.

Selroos O, Kuhlbäck B. Renal involvement in sarcoidosis. In: La Sarcoidose. Rapports du symposium européen de la sarcoidose (edit.Y Gallopin). Hallwag SA,Bern ,1972; pp 158-163 (199)**.**

Selroos and Kuhlbäck described four sarcoidosis patients with different renal manifestations verified by transcutaneous renal biopsies.
1) *acute interstitial nephritis,* i.e. mononuclear cells in abundance and some segmented granulocytes in the interstitial tissue, in a 26-year old man with acute sarcoidosis, bilateral hilar lymphadenopathy and erythema nodosum. The glomeruli, tubules and blood vessesls were normal. No granulomas were seen;
2) *chronic interstitial nephritis* with or without granulomas. A 35-year-old women developed renal calculi which were surgically removed. A biopsy specimen showed epithelioid cell granulomas consistent with sarcoidosis. Six months later lung infiltrates were found and the patient developed a nodule on her leg which showed granulomas. A Kveim test was positive. Five years later proteinuria and an impaired renal function were observed. A renal biopsy showed a chronic interstitial nephritis without nephrocalcinosis and granulomas at this time. Corticosteroids normalized the renal function. During a follow-up time of 12 years neither hypercalcaemia nor hypercalciuria developed;
3) *nephrocalcinosis*. A 33-year-old woman with pulmonary stage II sarcoidosis was treated with corticosteroids for eight months. Two years later she got joint pains and the chest radiograph revealed large exsudative infiltrates. Hypercalcaemia and renal failure were diagnosed. During treatment with prednisone the serum calcium values were normalized, but three months later a renal biopsy showed round-cell infiltration, fibrosis and nephrocalcinosis. Treatment with prednisone was continued for two years. A control renal biopsy showed no nephrocalcinosis; i.e. in patients with sarcoidosis nephrocalcinosis may be reversible during treatment with corticosteroids.
A fourth patient was a 38-year-old women who had an attack of renal colic and a recurrence four years later. Pulmonary stage II radiographic findings and uveitis were found. A scalene node biopsy showed epithelioid granulomas. The renal function was normal but hypercalciuria was noticed. Three years later an impaired renal function was diagnosed and after that radiographic nephrocalcinosis was seen. A renal biopsy showed serious changes; most glomeruli were hyalinized with perivascular fibrosis, the tubules were partially atrophic. The interstitial tissue was increased and infiltrated with mononuclear cells and calcareous deposits. Granulomas were not found.

During follow-up nephrocalcinosis remained, arterial hypertension developed and the renal function remained moderately impaired.

Jantunen E, Karjalainen L, Lampainen E, Aalto M-L. Sarkoidoosiin liittyvät munuaismuutokset (Sarcoidosis and renal manifestations). Duodecim 1994; 110:63-67 (in Finnish) (200). The authors described two patients with sarcoidosis who developed renal diseaes . The first patient, 47-year old, fell ill with skin lesions, and symptoms of urinary tract infection. Bilateral hilar lymphadenopathy was found. Granulomas were found in skin and bronchial biopsy specimens. The patient was treated with prednisolone. Two years later the patient developed renal insufficiency. A renal biopsy showed an interstitial nephritis and granulomas. Treatment with corticosteroids was started again and the renal function was more or less normalized.
The second patient, 35-year old, lost 7 kg of weight. Examinations revealed proteinuria, slightly elevated serum creatinine values, and enlarged hilar lymph nodes. Hypercalcaemia and hypercalciuria were found as well as increased values of serum ACE and lysozyme. A renal biopsy revealed nephrocalcinosis but no granulomas. After treament with corticosteroids for six months all laboratory values were normalized. Two years later sarcoidosis was considered inactive.

Putkonen T, Hannuksela M, Halme H. Calcium and phosphorus metabolism in sarcoidosis. Acta med sacand 1965; 177:327-335 (201). Putkonen et al described the metabolism of calcium and phosphorus in patients with sarcoidosis. They studied 60 patients with sarcoidosis; 42 female patients. Their mean age was 39.5 years (range 9-67). Thirty-one patients (52%) had skin lesions. Eighteen of 58 (31%) patients were skin test negative to 100 TU of PPD. The serum calcium mean values did nor differ from that of 100 control subjects. Only two patients had hypercalcaemia and at a 2-month follow-up all calcium values were normal. Serum phosphorus mean values (n=57) were significantly lower in the sarcoidosis group (mean 3.46±0.51 mg%) comparted with controls (n=75) 3.77±0.51 mg% ($p<0.01$). Eight sarcoidosis patients and two controls had serum phosphorus values <3.0mg%. Permanently depressed values were seen in two patients with chronic sarcoidosis. Serum magnesium values were normal in borh groups.

Repeated measurements of serum calcium concentrations were performed within the frame of a larger clinical epidemiological study. Hypercalcaemia was noted as follows (12): patients with pulmonary radiographic stage I lesions (n=73) mean value±SD 10.0±0.45 mg% (normal range 9-11 mg%) with six patients having mean values >11.0 mg%; stage II mean value 10.2±0.69 mg% with six patients having mean values >11.0 mg% (a further four patients had occasionally values >11.0 mg%); stage III mean value 10.1±1.28 mg% with one patients having a mean value of 12.9 mg%. The mean value of serum calcium in a control group of 45 subjects was 9.9±0.45 mg%. Hypercalciuria was found in 36 patients out of 107 (34%). Serum phosphorus mean values were significantly decreased in all three chest radiographic groups compared with control subjects.
In the series of Elo (18) hypercalcaemia was found in 13 patients of 304 (4.3%) and hypercalciuria in 33/195 (16.9%). In the series of Pietinalho 2.6% of the patients (n=502) had hypercalcaemia (21).

Sarcoidosis of the urinary bladder

Tammela T, Kallioinen M, Kontturi M, Hellström P. Sarcoidosis of the bladder: a case report and literature review. J Urol 1989; 141:608-609 (202). A case of bladder sarcoidosis in a women was presented. She had systemic sarcoidosis and biopsy of the urinary bladder showed a granulomatous inflammation of sarcoidosis type. The histological picture was different from malacoplakia as Michaelis-Gutmann bodies and dense aggregates of large mononuclear phagocytes were missing. After transurethral resection and treatment with corticosteroids the bladder lesion improved and the obstruction was relieved.

Sarcoidosis of the gastric mucosa

Järvinen M, Haahtela T, Mäkelä V. Kun sarkoidoosipotilaan mahaa kivistää ja hengitys vinkuu (Gastric pain and respiratory symptoms in a sarcoidosis patient). Duodecim 1988; 104:1546-1549 (in Finnish) (203). The authors desribed a patient with sarcoidosis for 15 years with pulmonary lymph node, ocular and liver involvement. During these 15 years the patient complained about gastric problems and diagnoses such as gastritis, diverticulitis, duodenal ulcer, side effects of corticosteroid treatment and

irritable colon syndrome. Finally a biopsy specimen of the gastric mucosa revealed a granulomatous inflammation consistent with sarcoidosis. The patient also developed shortness of breath. FEV1 was only 38% of the predicted normal value. Granulomas in the bronchial mucosa were found and bronchial hyperresponsiveness was detected. Tretment with corticosteroids did not affect the gastric symptoms but inhaled corticosteroids reduced the bronchial symptoms, improved lung function, but did not affect the bronchial reactivity.

Tukiainen H, Vaara J, Syrjänen K, Terho EO. Granulomatous gastritis as a diagnostic problem between sarcoidosis and other granulomatous disorders. Sarcoidosis 1988; 5:66-67 (204).
The authors described a 59-year-old man who suffered from achlorhydria and epigastric pain. A granulomatous lesion was found in the mucosa suggesting sarcoidosis or localized Crohn's disease. No signs of involvement of the terminal ileum or rectum were detected. A liver biopsy specimen showed changes suggestive of granulomatous inflammation. The patient was successfully treated with corticosteroids.

Involvement of the thyreoideal gland

Selroos O, Liewendahl K. Clinical manifestations of thyroidal sarcoidosis. In: La Sarcoidose. Rapports du symposium européen de la sarcoidose (edit.Y Gallopin). Hallwag SA, Bern 1972, pp.151-154. (205). The authors described four sarcoidosis patients with thyreoidal manifestations. 71-year-old lady, with congestive heart failure and residue after a cerebral stroke, who complained about lost of appetite, sweating and thirst. Twenty years earlier a resection of her thyroid gland had been performed due to thyreotoxicosis. When hospitalized erythema nodosum and bilateral hilar lymphadenopathy were seen. A Kveim test was positive and a diagnosis of acute sarcoidosis was established. Her symptoms were consistent with hyperthyreoidism which was confirmed with laboratory tests. Thyroid antibodies were found; the anti-thyroglobulin haemagglutinin titre was 1:2.5 milj. An open surgical biopsy was obtained from a hyperactive area of the thyreoidea and showed follicles with high follicular epithelium indicating hyperfunction, and furthermore epithelioid cell granulomas with giant cells consistent with sarcoidosis. She was treated with carbimazole and corticosteroids and achieved euthyroidism. This case represented acute sarcoidosis with granulomatous thyreoiditis in a hyperthyreoidal phase.
A second patient was a 51-year old woman with pulmonary stage II radiographic lesions and a small toxic nodular goiter.
The third patient, a 37-year old woman with a nontoxic goiter fell ill with acute sarcoidosis. Because of joint pains prednisone was given for one month. During a 2-year period sarcoidosis was cured but at this time thyrotoxicosis was found. Thyroid antibodies were not found and a biopsy of the thyroid gland did not reveal granulomas.
The fourth patient was a 55-year old woman with pulmonary sarcoidosis and thyreoiditis (high titres of thyroid antibodies) with hyperthyreosis. Five months after the hyperthyreoid phase she developed hypothyreoidism which was treated with substitution thyroxin therapy.

von Knorring J, Selroos O. Sarcoidosis with thyroid involvement, polymyalgia rheumatica and breast carcinoma. A case report. Scand J Rheum 1976; 5:77-80 (206). The authors described the follow-up of the 71-year-old woman described as patient no. 1 in reference no above. Three years after the diagnosis of sarcoidosis and thyreoditis with hyperthyreosis she developed polymyalgia rheumatic and breast carcinoma.. The associations and possible common mechanisms between the disorders were discussed.

Assendelft AHW, Kahlos T. Sarcoidosis of the thyroid gland. Sarcoidosis 1985; 2:154-156 (207). A thyroid tumour was suspected based on palpation status, ultrasound investigation and ^{99}Tc scan but samples taken at surgery showed thyroid sarcoidosis. Also a lymph node removed during surgery showed non-caseating epithelioid cell granulomas. After obtaining the histological verification of sarcoidosis a chest radiograph was taken and showed lesions consistent with sarcoidosis. Diffusion capacity for carbon monoxide (DL_{CO}) was lower than the reference value. Serum angiotensin converting enzyme activity and thyreoid stimulating hormone (TSH) were increased. The patient subsequently developed hypothyreosis and got substitution therapy.

Selroos O. Sarcoidosis with erythema nodosum, Löfgren's syndrome and granulomatous thyreoiditis. Report of 12 cases. Sarcoidosis Vasc Diffuse Lung Dis 2003; 22:243 (208). During a period of almost 40 years the aurthor observed 12 patients (11 women; age 38-72 years; nine were older than 60 years) with acute onset sarcoidosis, erythema nodosum, arthralgia and bilateral hilar lymphadenopathy. Two patients had also parenchymal infiltrates (stage II). In addition these patients had symptopms of thyreoid disease. Open biopsy or fine-needle aspiration biopsy showed epithelioid cell granulomas and a lymphocytic infiltration typical of granulomatous thyreoiditis. No other endocrine dysfunctions were noted. Four patients developed uveitis. At diagnosis serum ACE was elevated in six of seven tested patients, but in all 12 during follow-up. Thyroid antibodies were present in 10 of the 12 patients. At diagnosis seven patients showed hyperthyroidism, followed by hypothyroidism in four cases. Four patients were hypothyroidal at diagnosis. One patient (the male patient) was euthyreoidal from the beginning and remained so. Two tested patients were HLA DR3 (HLA DR17) positive, the HLA type usually associated with favourable prognosis in Scandinavian patients. However, only two patients exhibited the typical rapid resolution of the chest radiographic findings.

Grönhagen-Riska C, Fyhrqvist F, Välimäki M, Lamberg B-A. Thyroid hormones affect serum angiotensin I converting enzyme levels. Acta med scand 1985; 217:259-264 (111). The authors drew attention to the fact that thyroid hormons affect the determination of serum angiotensin-converting enzyme (ACE). Serum ACE was measured in 10 patients with Graves' disease and in two with thyroiditis during different stages of the diseases. The effect of thyroxine on serum ACE levels was also recorded in 12 patients with thyroid cancer, who were on thyroxine suppression. Serum ACE levels correlated positively with clinically assessed thyroid function and peripheral thyroid hormone levels, especially during hyper- or hypofunction. Serum ACE measurements may provide a useful tool for assessing thyroid function and the effect of thyroxine treatment.

Haematological manifestations

Koivunen E. Hematologiset löydökset sarkoidoosissa (Haematological findings in sarcoidosis). Academic dissertation, Acta Universitatis Tamperensis, Finland 1985 (in Finnish) (19).
Haematological data were available, partly retrospectively, in 990 patients (573 females) with a clinical picture of sarcoidosis. A total of 848 (86%) had histological evidence of epithelioid cell granulomas and/or a positive Kveim test. A further 54 patients had an increased activity of serum ACE to support the diagnosis. Anaemia was discovered in 5% of the males and 9% of the female patients. In the majority of cases anaemia was classified as secondary to sarcoidosis and was more frequent in patients with a short duration of symptoms (15%) compared to the rest of patients (3%). Of the females 5% has iron deficienct anaemia and 0.2% of the men. Autoimmune haemolytic anaemia was rare, although the direct antiglobulin test (Coomb's test) was positive in 5/390 patients compared to 0% in 1000 blood donors. In acute cases of short duration leukocytosis, eosinoiphilia, monocytosis and thrombocytosis were more often seen than in cases with a longer duration of disease. Neutropenia was noted in 6% of the cases with increasing frequency in cases with a longer duration of disease. The mean lymphocyte level in the whole series of patients was close to the lower limit of the reference level. Lymphopenia $<1.0x10^9$/l was discovered in 17% of the patients.
Ten percent of the patients had epithelioid cell granulomas in bone marrow specimens, more often patients with chronic sarcoidosis. Splenomegaly determined by spleen tomography was detected in 26% of the patients. Two % of those patients had a palpable spleen. Hypersplenism, was seen in 16% of the patients with an enlarged spleen.

Selroos O, Koivunen E. Prognostic significance of lymphopenia in sarcoidosis. Acta Med Scand 1979; 206:259-262 (209). In a series of 134 patients (20 with chronic disease)peripheral blood cells were counted. Patients with erythema nodosum had significantly increased monocyte levels. Lymphopenia $<1.0x10^9$/l was seen in 7.5% of the patients. Lymphocyte values $<1.5x10^9$ were common, especially in patients with long-standing disease. Significantly decreased lymphocyte counts were seen iun patients

>40 years of age, in patients negative to 10 TU of PPD and in those requiring treatment with corticosteroids. A correlation was found between low lymphocyte counts and a less favourable prognosis.

Koivunen E, Grönhagen-Riska C, Klockars M, Selroos O. Blood monocytes and serum and bone marrow lysozyme in sarcoidosis. Acta Med Scand 1981; 210:107-110 (96). The authors reported a significant positive correlation between peripheral blood monocyte counts and lysozyme concentration in patients with active sarcoidosis and increased activity of serum ACE.

Selroos O. Eosinophilia and sarcoidosis, Sarcoidosis 1904; 11: 80 (210). The author described six patients with blood eosinophilia out of a series of 140 patients with verified sarcoidosis. Their total number of neutrophils was within the normal range but eosinophils counted for 5-10%. No clinical symptoms of asthma or allergy were noticed. Lung function was normal in all six cases. Five to 12 years later five of the patients presented with clinical symptoms of asthma, one with an acute severe attack of asthma. Tests of airway function revealed obstruction which was >15% reversible with salbutamol inhalation. One patient was skin test positive to house dust mite and grass pollen. No signs of sarcoidosis were seen at the time of diagnosis of asthma.

Selroos O. Haemolytic anaemia and thrombocytopenia in sarcoidosis, Sarcoidosis Vasc Diffuse Lung Dis 1998; 15:83 (211). In a series of 140 patients with sarcoidosis two cases of haemolytic anaemia and five cases of thrombocytopenia were found. These patients were treated with corticosteroids due to the diagnosis of sarcoidosis. The haematological disturbances were normalized at the same time.

Haematological malignancies

Myeloma

Selroos O, Brander L, Virolainen M. Sarcoidosis and myeloma of lambda-type IgG. Acta med scand 1974; 195:59-63 (209). The authors described a 56-year old women who was diagnosed with bilateral hilar lymphadenopathy at the age of 48 years. A scalene lymph node biopsy showed epithelioid cell granulomas consistent with sarcoidosis. For years later bilateral uveitis was diagnosed. Further two years later, at the age of 52 years, the hilar lymphadenopathy had increased. A Kveim test was positive. Further investigations because of a high erythrocyte sedimentation rate (95 mm/h) releaved a myeloma of lambda-type IgG. In peripheral blood she had 84% T-cells and 14% B-cells. In vitro cultured lymphocytes were poorly stimulated with phythohaemagglutinin in the culture. Specimens of the bone marrow showed an increased proportion of plasmacells up to 15% of all nucleated cells. The was treated with melphalan but not with corticosteroids.

Pettersson T, Koivunen E, Ilvonen M, Jouppila J, Aalto E, Wasastjerna C. Sarcoidosis and multiple myeloma: an association. Br Med J (Clin Res Ed). 1987; 295(6604):958 (213). Five patients with sarcoidosis and myeloma were described; three males and two female patients (mean age 55 years, ragne 42-65). The diagnosis of sarcoidosis was based on both the clinical findings and histological evidence of non-caseating epithelioid cell granulomas in all five cases. In four patients myeloma developed several years after the diagnosis of sarcoidosis; in one both diagnoses were made at the same time. The duration of sarcoidosis was more than two years in three patients and sarcoidosis was considered to be active at the time of diagnosis of myeloma in two. Two patients had been treated with corticosteroids. All patients met the diagnostic criteria for multiple myeloma. Four patients were treated with cytotoxic drugs and one was followed without treatment. Four patients survived, but one died four years after the diagnosis of myeloma. The myelomas were of type IgG lambda in three cases, IgG kappa in one and IgA lambda in one case.

Lymphoma

Elo JJ, Klemi P, Nikkanen V. Sarcoidosis and malignant lymphoma in a same patient. Sarcoidosis 1986; 3(2):176 (214). Elo et al described a patient who at the age of 37 year developed Hodgkin's disease in a lymphnode. An enlarged spleen was removed. One year later the patient got erythema nodoum and a chest radiograph showed enlarged hilar lymph nodes and parenchymal infiltrations. Granu-

lomas were found in the bronchial mucosa and in mediastinal lymph nodes. A Kveim test was positive and serum ACE and lysozyme were increased. In three years sarcoidois was healed. Three years later Hodgkin's disease was reactivated. The further course was not described.

Partanen A, Pukkila S, Jantunen E. Sarkoidoosi-lymfoomaoireyhtymä (Sarcoidosis-lymphoma symptom complex). Duodecim 2016; 132: 661-665 (in Finnish) (215). The authors described three patients with malignant lymphoma. During the follow-up the patients developed lymphadenopathy. Histopathological examinations revealed granulomatous inflammation consistent with sarcoidosis. The association between sarcoidosis and lymphatic malignancies was discussed. However, the possibility of sarcoid-like reactions in association with malignancies was not discussed. The sarcoidosis-lymphoma syndrome poses a challenge for differential diagnosis particularly in the era of fluoro-deoxy-glucose positron emission tomography-computed tomography (FDG-PET-TT). Upon detection of enlargement of lymph nodes, the diagnosis should be confirmed with a histological sample.

Sarcoidosis of the skin and joints

Putkonen T. Skin sarcoidosis in Finland, In: Fifth international conference on sarcoidosis, Universita Karlova, (eds.L Levinský, F Macholda) Praha 1971:, pp 588-589 (216). Putkonen described a series of sarcoidosis patients from his Department of Dermatology. During the period 1950-1971 427 patients had been seen, among them 93 with skin lesions. There were 48 patients with scar sarcoidosis, 18 with popular or small nodular lesions, and 27 with large nodular, plaque-type or lupus pernio-type skin lesions.

Putkonen T, Virkkunen M, Wager O. Joint involvement in sarcoidosis with special reference to the coexistence of sarcoidosis and rheumatoid arthritis. Acta rheum scand 1965; 11:53-61 (217). In a group of 94 cases of sarcoidosis one definite and one probable case of rheumatoid arthritis was found. Additionally, the radiographic findings on the digital phalanges were in some of the patients similar to those in rheumatoid arthritis. Signs of rheumatoid arthritis were no more frequent than would be expected in a group of subjects of equal size without sarcoidosis. The most common form of joint involvement in sarcoidosis was migratory polyarthritis, which in cases of subacute sarcoidosis had an incidence of 33 per cent, and in association with erythema nodosum 57 per cent. Difficulties of differential diagnosis will arise mostly with respect to rheumatic fever, especially when the disease begins with joint symptoms and fever. In such atypical cases of arthritis the Kveim test was of diagnostic value.

Tattoo reactions

Kluger N. Cutaneous complications related to tattoos: 31 cases from Finland. Dermatology. 2017; 233:100-109 (218). In a tattoo series from Finland consisting of 31 patients (15 women) with complications, sarcoidosis was detected as complication in one patient (3%). This review is the largest series of tattoo complications in the Baltic area. It illustrates the wide spectrum of complications. Prospective, controlled therapeutic studies are necessary to assess the best treatment protocols for tattoo allergies and tattoo reaction management in general.

Lymphoedema

Putkonen T, Hannuksela M. Alaraajojen krooninen lymfödeema sarkoidoosissa (Chronic lymphoedema of the lower extremities in sarcoidosis). Duodecim. 1967; 83:86-88 (in Finnish) (219). The authors published a case report on a patient with sarcoidosis and enlarged pelvic and inguinal lymph nodes, detected by lymphography, and resulting in chronic lymphedema of the lower extremities. These lymph nodes, as well as the hilar lymphadenopathy, diminished spontaneously during a 2-year follow up. The lymphographgic findings normalized, too.

Sarcoidosis of the nose

Selroos O, Niemistö M. Sarcoidosis of the nose. Including a report on a patient with large sarcoid polypi of the nasal mucosa. Scand J Respir Dis 1977; 58:57-62 (220). A report was presented on 11 patients with histologically confirmed nasal sarcoidosis, including one case with very large nasal polypi. The most frequent symptom was obstruction of the nose followed by dryness and crusting. Thickening of

the nasal mucosa was the most frequent finding. Yellowish dots were observed in four patients and polypi in two. In one patient, a granulomatous maxillary sinusitis was diagnosed. Cutaneous sarcoidosis was found in only one patient. Nine of the patients had noted their nasal symptoms during the early phase of the disease. The response to treatment with corticosteroids was discussed. It appeared that an enquiry about nasal symptoms and examination of the nasal cavity were valuable even in patients with early sarcoidosis.

Concomitant diseases

Reunala T, Collin P. Diseases associated with dermatitis herpetiformis. Br J Dermatol. 1997; 136:315-318 (221). The occurrence of associated diseases in a cohort of 305 patients with dermatitis herpetiformis (DH) followed up for a mean of 10 years was studied. The results were compared with those from 383 patients with coeliac disease (CD). Twenty-nine (9.5%) patients with DH and 73 (19.1%) with CD had concomitant endocrine or connective tissue disorders. The following associations were found: auto-immune thyroid disease (4.3% of DH patients and 6.0% of CD patients), insulin dependent diabetes (1.0% DH and 5.5% CD), lupus erythematosus (1.3% DH and 0.3% CD), Sjögren's syndrome (1.0% DH and 2.9% CD), *sarcoidosis* (1.3% DH and 1.8% CD), and vitiligo or alopecia areata (1.6% DH and 0% CD

Treatment of pulmonary sarcoidosis

Putkonen T. Therapeutical experiments with penicillin in lymphogranulomatosis benigna Schaumann. Acta dermatovener (Stockholm) 1948; 28:171-173 (222). The results of a small clinical trial in sarcoidosis were reported by Putkonen. He treated three patients who had chronic skin lesions and pulmonary, partly fibrotic lesions. Two patients had involvement of the nasal mucosa, two osseous lesions in the digital phalanges, and two had lymphadenopathy. The patients were treated with penicillin intramuscularly for two to three weeks. No changes in the clinical picture were observed.

Peltola P, Koskimies A. Effect of long-term cortisone therapy on pulmonary sarcoidosis. Ann Med Intern Fenn 1960; 49:100-110 (223). In 1955-1960 the authors saw 30 patients (16 male, 14 female patients) with biopsy-proven sarcoidosis. Nineteen patients had a disease duration with symptoms of less than 1½ years; 11 patients had had symptoms for 1½-9 years. Thirteen patients (seven males) were treated with cortisone 50-75 mg or predisone 10-15 mg per day; 17 patients (eight males) constituted a control group. The mean observation time from first symptoms to start of treatment was 4 years and 7 months (1-9 years). In the untreated control group the corresponding mean time was 5 years and 10 months (1-12 years). In term of improvements in chest radiographic findings and lung function tests the difference between the groups in favour of the treated patients was impressive. The mean observation time for treatment was 8.5 months; range 3 months to 3 years.

Selroos O, Sellergren T-L. Corticosteroid therapy of pulmonary sarcoidosis. A prospective evaluation of alternate day and daily dosage in radiographic stage II disease. Scand J Respir Dis 1979; 60:215-221 (224). Thirty-nine sarcoidosis patients with pulmonary infiltrations (stage II) of less than 5 years duration and not treated earlier with corticosteroids were randomly allocated for treatment with methylprednisolone for 7 months or for observation without therapy. Every other treated patient was given the drugs daily and every other followed an alternate-day regimen. After 7 months the chest radiographic finding, the forced vital capacity (FVC) and the diffusion capacity for carbon monoxide (DLCO) were superior in the treated group. There was no difference between the two drug regimens. After 24 and 48 months no statistically significant differences between the untreated and the treated groups were found.

Selroos OB. Use of budesonide in the treatment of pulmonary sarcoidosis. Ann N Y Acad Sci 1986; 465:713-721 (225). Twenty patients with active sarcoidosis, increased serum ACE activity, and progressive pulmonary disease (stages II and III) were treated for 18 months with inhaled budesonide instead of oral corticosteroids in an open clinical study. The daily dose of budesonide was 800 μg or 600 μg twice

daily for 3-6 months administered via a tube spacer. Thereafter the daily dose was reduced to 800 µ and further to 400 µg per day. A general improvement in chest radiographic findings and in forced vital capacity was noted. Serum ACE activity was normalized.

Selroos O. Use of budesonide in the treatment of pulmonary sarcoidosis. In: Advances in the use of inhaled corticosteroids (eds. R. Ellul-Micallef, W.K. Lam, J.H. Toogood) Hong Kong, Excerpta Medica Asia Pacific Congress Series no 58, 1987:pp 188-197 (226). In addition to the open 18-month study presented above (221) this paper included the results of treatment with inhaled budesonide, 1200 to 2400 µg per day in 12 patients with relapsing sarcoidosis – a clinical condition where spontaneous remissions are rarely seen. A normalization of the radiographic lesions was seen in two patient, marked radiographic improvement in three patients, a moderate improvement in two patients, slight improvement in one. The radiographies were unchanged in three patients and deteriorated in one. Treatment continued for six to 27+ months. Improvements in forced vital capacity (FVC) and diffusion capacity (DLCO) were noted, as weel as improvements in markers of disease activity (serum ACE and lysozyme) and in ^{67}gallium scans. The three patients not improving after six months on budesonide were given oral steroids in addition. The patient with deteriorating lung status was treated with oral methylprednisolone 48 mg per day.

Erkkilä S, Fröseth B, Hellström P-E, Kaltiokallio K, Taskinen E, Viljanen A, Viljanen B, Selroos O. Inhaled budesonide influences cellular and biochemical abnormalities in pulmonary sarcoidosis. Sarcoidosis 1988; 5:106-110 (74). In a randomized, double-blind, placebo-controlled study 19 patients with newwly-detected pulmonary sarcoidosis were gtrteated with inhaled budewsonide, 800 µg twicew daily (n=9) or placebo (n=10) for 8-10 weeks. Before and after treatment chest radiographs, lungfunctionb tests, bronchoalveolar lavage (BAL) and biochemical markers of activity were performed. No significant changes were seen in the chest radiographs or lung function tests during this short period of time. In the budesonide-treated group significant decreases in serum ACE and lysozyme and in BAL hyaluronan were seen, as well as a decrease in the percentage of BAL T-lymphocytes and in the T4/T8 lymphocyte ratio. No changes were seen in the placebo group.

van den Bosch JJM, Westermann CJJ, Aumann J, Edsbäcker S, Tönnesson M, Selroos O. Relationship between lung tissue and blood plasma concentrations of inhaled biudesonide. Biopharm Drug Dispos 1992; 14:455-459 (227). 1600 µg of budesonide was given preoperatively to 11 patients undergoing lung surgery for lung cancer. Blood and tissue samples for determination of budesonide were obtained before and during thoracotomy at various periods of time. The mean budesonide concentration in lung tissue compared with the concentration in blood plasma was 8.7 times higher. Owing to technical reasons there was a time difference (range -90 min to +60 min) between sampling of lung specimens and sampling of plasma. However, regression analysis of the two sets of data showed that lung and plasma levels fall almost in parallel. At 150 min (the mean sampling time) the two lines differed by a factor of 7.9. The results seemed to indicate that lung parenchymal lesions can be treated with inhaled drugs.

Selroos O, Löfroos A-B, Pietinalho A, Niemistö M, Riska H. Inhaled budesonide for maintenance treatment of pulmonary sarcoidosis. Sarcoidosis 1994; 11:126-131 (228). Forty-seven patients with pulmonary sarcoidosis stage II-III, fulfilling clinical indications for starting treatment with corticosteroids, received oral methylprednisolone for 8 weeks in gradually decreasing doses. From week 5 onwards they also receivewd inhaled budesonide, 1600 µg daily. Treatment was continued for 18 months and all patients have been followe up for 3 years. At 18 months treatment could be discontinued in 38 patients, who had used individually adjusted doses of budesonide depending on the clinical response. Budesonide treatment alone was satisfactory in 31 of those 38 patients. An additional seven patients could stop treatment after receiving supplementary courses of oral steroids for 3-12 months. Chest radiohgraphs became normal in 22 patients and improved in 14. Significant improvements were noticed in lung function tests (FVC, DL_{CO}) in relation to prfedicted normal values. Serum ACE, lysozyme and β_2-microglobulin values decreased significantly. Transient cough was seen in five patients and hoarseness

in three. No systemic side-effects were registered. The study indicated that inhaled budesonide may offer an effective and safe alternative to oral steroids for long-term maintenance treatment of pulmonary sarcoidosis.

Pietinalho A, Tukiainen P, Haahtela T, Persson T, Selroos O. Oral prednisolone followed by inhaled budesonide in newly diagnosed pulmonary sarcoidosis. A double-blind, placebo-controlled, multicenter study. Chest 1999; 116:424-431 (229). This was a double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy of oral prednisolone, followed by inhaled budesonide, in patients with newly diagnosed (duration of disease <3 months) stage I and stage II pulmonary sarcoidosis. One hundred eighty-nine adult patients were randomized to treatment. Patients with erythema nodosum or stage IV sarcoidosis (pulmonary fibrosis), and patients requiring immediate treatment with oral corticosteroids for extrapulmonary lesions or chronic illnesses were excluded. The patients received either oral prednisolone for 3 months (20 mg/d for 8 weeks, 15 mg/d for 2 weeks, and 10 mg/d for 2 weeks) followed by inhaled budesonide for 15 months at 800 μg bid, or placebo tablets followed by placebo inhaler therapy. Chest radiographs, lung volumes (FVC), diffusing capacity for carbon monoxide (DLco), serum angiotensin-converting enzyme (ACE), and β_2-microglobulin were obtained at 3-month intervals. After 3 months of treatment, radiographic improvements were seen in the active-treatment group when compared to the placebo-treatment group. At 6 months, the difference was still statistically significant. Later, no differences were found. In patients with initial stage I lesions, neither the FVC nor the DLco (the percent predicted mean values) changed during the study, as they were normal from the beginning. In patients with initial stage II disease, the difference in the FVC mean values between the groups also remained unchanged throughout the study. In stage II patients treated for 18 months, but not earlier, the difference in DLco became statistically significant; the largest differences were seen in patients with initial FVC values <80% of predicted and DLco values <75% of predicted. The decrease in ACE in the active-treated stage II patients was significantly greater than in the placebo-treated patients. No difference was observed in adverse events between the active-treated patients and the placebo-treated patients. An initial treatment with prednisolone followed by long-term inhalation of budesonide was more effective than placebo in patients with stage II disease. Sequential oral and inhaled corticosteroid therapy may be an alternative treatment regimen for stage II sarcoidosis patients, rather than long-term oral corticosteroid therapy alone.

Pietinalho A, Tukiainen PS, Haahtela T, Persson T, Selroos O. Early treatment of stage II sarcoidosis improves 5-year pulmonary function. Chest 2002; 121:24-31 (230). This was a follow-up study of ref. 227 above evaluating the 5-year prognosis of patients with stage I and stage II newly detected (<3 months) pulmonary sarcoidosis treated immediately after diagnosis with prednisolone for 3 months followed by inhaled budesonide for 15 months. One hundred forty-nine patients were followed up for 5 years: 79 patients with initial stage I disease and 70 patients with stage II disease. Oral prednisolone was given for 3 months followed by inhaled budesonide for 15 months (800 μg bid), or placebo tablets followed by placebo inhaler therapy.Thereafter, treatment was given only on an individual basis in the case of clinical deterioration. Yearly follow-up visits were performed with chest radiographs, lung function tests (FEV_1, FVC), diffusion capacity of the lung for carbon monoxide (DLco), serum angiotensin-converting enzyme (ACE), and serum and urinary calcium measurements. No initial differences were observed in chest radiographic findings between the active-treatment and placebo-treatment groups, either in patients with initial stage I or stage II disease. However, after the 5-year follow-up, 18 steroid-treated patients (26%) and 30 placebo-treated patients (38%) still had remaining chest radiographic changes. Placebo-treated patients more frequently required treatment with corticosteroids during the 5-year follow-up ($p<0.05$).Steroid-treated patients with initial stage II disease improvedmore in FVC and DLco ($p<0.05$). No differences were seen in reported adverse events or in ACE, serum calcium, or urinary calcium values. Immediate treatment of pulmonary stage II sarcoidosis - but not of stage I disease - improved the 5-year prognosis with regard to lung function variables.

Prognosis of sarcoidosis

Selroos O, Wegelius O. The prognosis of early pulmonary sarcoidosis. Scand J Respir Dis 1966; 47:195-199 (231). The report deals with 59 sarcoidosis patients seen from 1959 to 1964. A total of 32 patients had radiographic stage I lesioins (18 with concomitant erythema nodosum), and 27 stage II (three patients with erythema nodosum). A total of 31 patients had been treated with prednisolone, as was the recommendation in the early 1960's. After ≤1 year of follow-up, 24 of the 59 patients (39%) had a normal chest radiographic finding, 26 (42%) had improved, eight (13%) were unchanged and one patient had deteriorated. After 1-2 years (n=51) the chest radiograph was normal in 34 patients (67%), improved in 14 (27%), unchanged two (4%), and deteriorated in one (2%).

Selroos O. The frequency, clinical picture and prognosis of pulmonary sarcoidosis in Finland. Acta Med Scand 1969 suppl 503 (12). A total of 140 patients were included in the prognosis evaluation: 91 untreated patients (stage I 59, stage II 32), and 49 patients who received treatment with oral corticosteroids for various periods of time (stage I 20 patients, stage II 29). Pulmonary lesions alone were seen in 10 and 22 of these treated patients. In sarcoidosis stage I the prognosis was found to be good, especially in cases presenting with erythema nodosum. When corticosteroid treatment was administered, resolution of the lesions was more rapid during the first year, but at the end of the second year no significant difference was observed. The prognosis was also considered favourable at stage II, although not as good as at stage I. Spontaneous healing of the lesions required a longer period of time, and the difference between untreated and treated patients was therefore more marked after one year of observation. After two years the difference between the two groups was minimal. It thus appeared that at stages I and stage II the prognosis was not appreciably influenced by treatment. The group of patients showing extrapulmonary manifestations of sarcoidosis had a less favourable prognosis.

Hannuksela M, Salo OP, Mustakallio KK. The prognosis of acute untreated sarcoidosis. Ann Clin Res 1970; 2:57-61 (232). In a series of 135 patients the prognosis of acute untreated sarcoidosis was studied. The interval from first symptoms or last normal chest radiograph was six months or less. The follow-up period varied between seven months and nine years. Seventy-six percent of the cases healed completely within two years. Erythema nodosum, youth, hilar adenitis without lung changes, high tuberculin sensitivity and in some degree also female sex seemed to favour a good prognosis. Previous BCG vaccination and the presence of scar sarcoidosis did not seem to be of prognostic significance.

Selroos O, Niemistö M, Riska N. A follow-up study of treated and untreated early pulmonary sarcoidosis. Proceedings of the VI International Conference on Sarcoidosis (eds. K Iwai, Y Hosoda), University of Tokyo Press, 1973, pp 525-528 (233). During the years 1960-1966 a total of 132 patients were diagnosed with sarcoidosis. A total of 115 patients took part in a follow-up examination in 1971. Because of a change in the attitude towards the use of corticosteroids in sarcoidosis, it was possible to divide this series into two: untreated (n=87) and treated patients (n=48). Results were reported after follow-ups for one year, two years and five years. In patients with initial pulmonary radiographic stage I disease (n=46) the results were as follows: the number and per cent of normal chest radiographic findings after one year was 14 (30%), after two years 27 (59%), and after five years 43 (93%). The corresponding figures for the treated patients (n=21) were: after one years 11 (52%), after two years 18 (86%), and after five years 18 (86%). For patients with initial stage II radiographic lesions (n=48) normalization the the chest radiographic changes in untreated patients was seen after one year in 3 (13%), after two years in 10 (43), and after five years in 20 patients (87%). For treated patients the correspondoing figures were: after one year 8 (32%), after two years 16 (64%), and after five years 20 (80%). The prognosis of early pulmonary sarcoidosios was favourable. The initial occurrence of erythema nodosum, high tuberculin sensitivity, age below 40 years and female sex favoured an especially good prognosis. The utility of corticosteroids was no more than suppressive during the initial phase of the disease, and led to false conception of its favourable effect. It also seemed probable that the risk of recurrence and of chronicity of the disease increased if corticosteroids had been

administered, particularly if they had been given for only 4-6 months.

Selroos O, Koivunen E. Prognostic significance of absolute lymphopenia in sarcoidosis. Acta med scand 1979; 206:259-262 (209). During 1959-1967, sarcoidosis was diagnosed in a series of 140 patients. All were followed up and 22 developed chronic sarcoidosis. In 134 patients (20 with chronic course) the initial granulocyte, monocyte and lymphocyte counts were known. No differences in granulocyte values were seen between different groups of sarcoidosis patients. Patients with erythema nodosum had significantly increased monocyte levels. Lymphopenia below 1 000/µl was seen in only 7.5% of the patients. Lymphocyte counts below 1 500 µl were a common finding, especially in patients developing chronic sarcoidosis. Significantly decreased lymphocyte values were also seen in patients older than 40 years at the time of diagnosis, in patients negative to 10 TU of PPD and in those with a disease requiring treatment with corticosteroids. A correlation was found between initial lymphopenia and less favourable prognosis, 85% of the patients having a very good prognosis. Patients with initial lymphopenia must be carefully followed up. The initial presence of erythema nodosum does not always guarantee a good prognosis.

Elo JJ. Sarkoidoosi – ennuste. In: Sarkoidoosi. Kliininen tutkimus Varsinais-Suomen tuberkuloosipiirissä vuosilta 1965-1977. (Sarcoidosis - prognosis.In: A clinical study in a tuberculosis district in south-western Finland in 1965-1977), University of Turku, 1981 (18). Elo reported a series of 356 sarcoidosis patients seen at the Paimio hospital. The series was divided into two: 185 patients diagnosed in 1965-1973 with radiographic follow-up data available in 122 cases in 1976-1980. A total of 171 patients were diagnosed in 1974-1977 and followed according to a predetermined scheme. Of the 122 patients in the earlier group 33 (27%) had a normal chest radiograph at the follow up. One patient still had an active disease. Fibrosis in the hilar region was seen in 12 patients (10%), central fibrosis in 43 (35%) and more widespread fibrosis in 32 (26%). In the later series (n=157) 321 patients (20%) had a normal chest radiograph at the follow up, two had an active disease, 30 patients showed fibrosis in the hilar region (19%), 47 and 47 patients central or widespread fibrosis (30% each). Four patients with stage III pulmonary lesions at the time of diagnosis had died during the follow-up.

Huhti E, Poukkula A, Lilja M. Prognosis for sarcoidosis in a defined geographical area. Br J Dis Chest 1987; 81:381-390 (234). One hundred and ninety-nine cases of sarcoidosis were diagnosed from July 1970 to December 1976 in a defined geographical area in northern Finland. At the follow-up examination at least 5 years later (range 5-12 years) a chest radiograph was obtained from 179 patients (90%) and lung function tests were performed by 169 patients (85%). A normal radiograph was achieved by 94 of the 113 patients with stage I sarcoidosis (83%), and by 36 of the 62 patients with stage II (58%). Two patients in the former group (2%) and 14 in the latter (23%) had progressed to the fibrotic stage Ill, but the fibrosis was usually slight. FEV_1 and FVC increased during the follow-up period, DLCO showed the largest number of abnormal results in the final examination. Lung function largely normalized with a normal radiograph, whereas the functional outcome was worst where fibrosis had developed. Only two patients had been granted a disability pension because of sarcoidosis. Six patients had died, but none of sarcoidosis. The results showed a favourable prognosis for sarcoidosis.

Tukiainen P, Taskinen E, Riska H. The prognostic value of bronchoalveolar lavage in sarcoidosis. Sarcoidosis. 1994; 11:69-72 (78). The authors studied 237 consecutive patients with recently diagnosed sarcoidosis who had adequately long follow-up to be evaluated. One hundered and sixty-six patients were followed for at least one year, and 64 for at least two years. The clinical variables showing a highly significant ($p<0.0001$) correlation with unfavourable prognosis were age >50 years, duration of symptoms >6 months, absence of erythema nodosum, and hilar lymphadenopathy together with moderate or marked parenchymal opacities. Pulmonary function variables were related to prognosis less significantly. The bronchoalveolar lavage findings showing most significant ($p<0.01$) correlations with unfavourable outcome were elevated total cell count, high CD8+ T-cell count, high albumin and IgG content. High lymphocyte count, low CD4+Th/CD8+Ts cell ratio

and high IgG/albumin ratio showed only marginal (p<0.03-0.07) correlation with unfourable prognosis. In logistic regression analysis high IgG content and high CD8+ Ts cell counts were the variables entering in to the model of unfavourable prognosis.

Milman N, Selroos O. Pulmonary sarcoidosis in the Nordic countries 1950-1982. II. Course and prognosis. Sarcoidosis 1990; 7:113-118 (235). The authors summarized data from the Nordic countries and described similarities ansd differences. Overall the prognosis was favourable. Cases with acute onset with chest radiographic stage I, fever, arthritis and erythema nodosum had a 85-90% remission rate during the first two years. The overall five year remission rate for stage I was 82%, stage II 66%, and stage III 30%. Among patients with stage I, 2-5%, and among cases with stage II and III, 6-10% developed chronic pulmonary disease. Patients with stage I had a normal mortality rate whereas those with stage II, III and IV has a rate threefold higher than expected due to sarcoidosis-related cardio-pulmonary complications.

Pietinalho A, Ohmichi M, Löfroos A-B, Hiraga Y, Selroos O. The prognosis of pulmonary sarcoidosis in Finland and Hokkaido, Japan. A comparative five-year follow-up study of biopsy-proven cases. Sarcoidosis Vasc Diffuse Lung Dis 2000; 17:158-166 (236). This study compared the 1-5 year prognosis between Finnish and Japanese (Hokkaidoan) patients with sarcoidosis. In the Finnish series of patients (n=437) a complete normalization of chest radiographic findings occurred in 40% of the patients. Of the 191 Finnish patients with radiographic stage I lesions normalization was seen in 47% (50% in patients with concomitant erythema nodosum). In 186 Finnish patients with stage II disease normalization of the chest radiography was seen in 36% of the patients. Overall the Japanese patients had a significantly more favourable prognosis compared with the Finnish patients regarding age, sex, and symptoms, chest radiographic and extrapulmonary lesions.

Sarcoidosis and pregnancy

Selroos O. Sarcoidosis and pregnancy: a review with results of a retrospective study. J Intern Med 1990; 227:221-224 (237). This was a report on 55 patients with sarcoidosis and 69 pregnancies in relation to outcome. The information was divided into three sections:

First appearance after pregnancy. Twenty-five patients were found to have sarcoidosis within one year after delivery. Twelve patients fall ill with erythema nodosum, and one with arthralgia. Six patients were found to have pulmonary manifestations at routine chest radiography. Five patients had respiratory symptoms and one patient enlarged peripheral lymph nodes. Most patients recovered spontaneously within two years; three required treatment with corticosteroids.

Pregnancy in patients with active sarcoidosis. Eighteen patients with active sarcoidosis had a total of 26 pregnancies during a follow-up period of 29 years. After pregnancy the chest radiographs were normal in 12 cases, improved in three, was unchanged in nine and deteriorated in two women. Improvement of sarcoidosis is often seen during pregnancy. However the disease could progrediate after pregnancy and during the lactation period. After the 26 pregnancies in this report seven patients deteriorated during the first year after delivery; in five of them already within four months.

Pregnancy in patients with inactive sarcoidosis. Twelve women with 18 pregnancies belonged to this category. Some of the patients had some remaining changes in their chest radiographs but lung function measurements were within the reference ranges. No deteriorations occurred during these pregnancies.

Pregnancy usually had a favourable effect on sarcoidosis but relapses occurred after delivery. Pregnancy in women with poor lung function needs thorough investigations and careful observation during pregnancy. Termination of pregnancy due to a deleterious effects on sarcoidosis in general, or due to adverse effects of the disease on pregnancy or foetus, are rare events.

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Index of Finnish Authors