ASPECTS OF THE PATHOGENESIS OF EXTRAPULMONARY TUBERCULOSIS WITH SPECIAL REFERENCE TO TUBERCULOUS ARTHRITIS

An epidemiological case-analysis and a cohort follow-up study

ASPECTEN VAN DE ONTSTAANSWIJZE VAN EXTRAPULMONALE TUBERCULOSE IN HET BIJZONDER TUBERCULEUZE GEWRICHTSONTSTEKING

Een epidemiologische analyse en een cohort vervolgonderzoek

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof.dr.P.W.C. Akkermans M.A. en volgens het besluit
van het College voor Promoties. De openbare
verdediging zal plaatsvinden op
woensdag 14 december 1994 om 13.45 uur

door

CORNELIS ADRIANUS POSTEMA

geboren te Eindhoven

PROMOTIECOMMISSIE

PROMOTOR: Prof.dr.J.Huisman

OVERIGE LEDEN: Prof.dr.C.Hilvering
Prof.dr.P.J.van der Maas
Prof.dr.L.B.A. van de Putte

Op de omslag een afbeelding uit "Tuberculose osseuse et osteo-articulaire" Edition Et. Sorrel 1932.
Collectie Museum Boerhaave, Leiden.

Omslag ontwerp: Ineke Keesom
Lay-out: Rob Gaarenstroom

CIP-GEGEVENS KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Postema, Cornelis Adrianus

Aspects of the pathogenesis of extrapulmonary tuberculosis with special reference to tuberculous arthritis : an epidemiological case-analysis and a cohort follow-up study / Cornelis Adrianus Postema. - Amstelveen : Ziekenfondsraad
Thesis Rotterdam. With ref. - With summary in Dutch.
ISBN 90-70918-11-0
Subject headings: tuberculosis.

De totstandkoming van dit proefschift werd financieel mede mogelijk gemaakt door een bijdrage van de KNCV.

"We have come to a point where we hardly could hope for more success. We must make new researches. Such researches will open new fields, new theories, new modes, and possibilities of fighting the old enemy, tuberculosis".

Robert Koch, New York, 11 april 1908.

voor Douwe & Sanne

Contents

List of abbreviations

AA	Adjuvant arthritis
AIDS	Acquired Immuno Deficiency Syndrome
ALS	Anti-lymphocyte serum
BCG	Bacille Calmette Guérin
CD	Cluster of differentiation
CFA	Complete Freund's adjuvant
CWF	Cell wall fragments
EB	Epstein-Barr
gp	glycoproteine
GBM	Glomural basement membrane
HIV	Human Immunodeficiency Virus
HLA	Human leucocyte antigen
HNP	Herniated nucleus pulposus
HSP's	Heat-shock proteins
i.a.	intra-articular
IFA	Incomplete Freund's ajuvant
IFN	Interferon gamma
IL-1	Interleukine-1
LPS	Lipopolysaccharide
MDP	Muramyldipeptide
MHC	Major histocompatibility complex
MIP	Metacarpo-phalangeal joints
OVA	Ovalbumin
PHS	Periarthritis Humeroscapularis
PIP	Proximal interphalangeal joints
PG	Peptidoglycan
RA	Rheumatoid arthritis
RFLP	Restriction fragment length polymorphism
RMOH	Regional Medical Officer of Health
SCW	Streptococcal cell wall
SLE	Systemic lupus erythematosus
TB	Tuberculosis
TNF	Tumour necrosis factor

I. *Introduction*

On August 15th 1988 a former general practitioner from the municipality Veghel reported to the Regional Medical Officer of Health of the Province North Brabant that since May 1987 in at least 8 of his patients tuberculosis (tb) had been diagnosed. Thereupon the Medical Officer started an official investigation.

Soon it was clear that the problem was not limited to the 8 reported cases but that the magnitude of the explosion was much more extensive than supposed. From the beginning the aetiology of this event was far from clear.

In January 1990 an official report was published by the Chief Medical Officer's Department of Infectious Diseases, entitled "Rapport aan de Geneeskundig Inspecteur van de Volksgezondheid voor Noord Brabant inzake de explosie van voornamelijk extrapulmonale tuberculose bij patienten in behandeling bij een arts te Veghel" (1). This report included an epidemiological analysis of the explosion. Eventually a total of 55 cases of predominantly extrapulmonary tuberculosis were diagnosed.

In the summary of the report some remarks were made with regard to the pathogenesis of the explosion. It was suggested that the most likely cause of the event was an exogenous (re)infection with haematogenous spread to a so called "locus minoris resistentiae" i.e. a location with diminished (immunological) resistance.

In the closing remarks of the Report the hope was expressed that in the near future more data would become available that could make the mechanisms that have played a role in this explosion more clear.

In this thesis some aspects of bacterial especially tuberculous arthritis are discussed in connection with an outbreak of extrapulmonary tuberculosis in patients who were visiting an outpatient department for rheumatic diseases.

An epidemiological analysis provides many details of the explosion originating in Veghel. Also a cohort follow-up study was performed with regard to the pathogenesis and the results are presented in this thesis.

Reference

1. Geneeskundige Hoofdinspectie van de Volksgezondheid afdeling infectieziekten. Rapport aan de Geneeskundig Inspecteur van de Volksgezondheid voor Noord Brabant inzake de explosie van voornamelijk extrapulmonale tuberculose bij patienten in behandeling bij een arts in Veghel. 1990; januari Rijswijk.

II. Arthritis

II.1. The normal joint

The joints are ideally constructed to serve their function as the hinges of the skeletal system. Each consists principally of two molded, contoured ends of bone shaped to permit motion of one bone upon the other (figure II.1). The bones are connected through a sleeve of dense collagenous connective tissue, the joint capsule. This capsule is further supported and buttressed by ligaments and tendons. The exposed ends of the bone within the joint space are covered by a thin layer of hyaline articular cartilage that provides a smooth gliding surface. Ease of motion is further provided by a thin glistening lining epithelium, the synovial membrane and by its secretion, a viscid, clear, white to yellow synovial fluid.

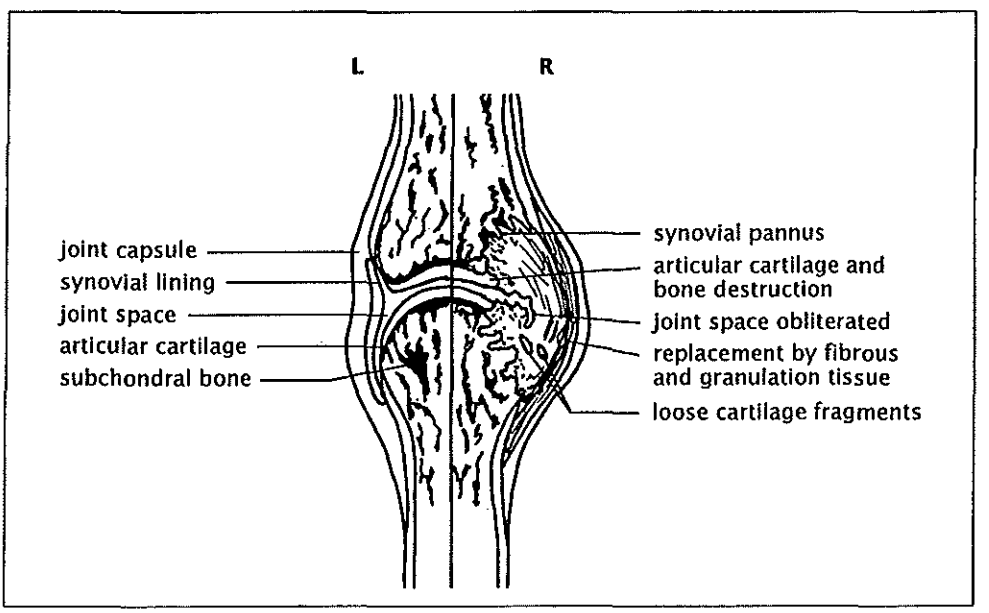

Figure II.1. Synovial joint. Left: normal condition. Right: inflammatory changes in rheumatoid arthritis.

The synovium is derived from mesenchyme. In areas subjected to direct weight-bearing, the membrane consists of a single layer of flattened, almost invisible pavement cells resembling to a considerable extent the mesothelial lining of the body cavities. In areas subjected to less stress, these cells are cuboidal and more readily visualised and often contain small cytoplasmic vacuoles as indicators of their secretory function. The synovial epithelium is not only secretory, but also serves the important function of transferring fluids and electrolytes into and out of the joint space as well as somewhat larger molecules or particles which may accumulate here as the result of injury or infection.

In this fashion permanently lubricated hinges are provided. But it is not surprising that such structures, in constant use, often subject to excessive strains and stresses, should be the site of frequent injury and degenerative wear and tear (28).

II.2. Arthritis

Arthritis can be divided into acute and chronic forms and can be produced by a wide range of conditions. Acute arthritis is defined as an arthritis with significant features of inflammation of less than 14 days duration (27).

II.2.1. Acute Arthritis

The differential diagnosis of acute arthritis is shown in table 1.

Table 1.

1. Acute bacterial infections	
2. Crystal-induced diseases	▪ Gout ▪ Calcium pyrophosphate arthropathy ▪ Calcium hydroxyapatite arthropathy
3. Trauma	
4. Spontaneous haemarthros	▪ Clotting disorders ▪ Anticoagulants ▪ Local synovial abnormalities e.g.pigmented villonodular synovitis
5. Reactive arthritis	
6. Acute osteomyelitis close to a joint	
7. Local soft tissue lesion	▪ Infection ▪ Crystal induced ▪ Trauma
8. Initial phase of a chronic disorder	▪ Rheumatoid arthritis ▪ Psoriatic arthritis ▪ Ankylosing spondylitis ▪ Osteoarthritis ▪ Systemic Lupus Erytematosus (SLE)

The principle causes are mentioned in the table but the list is not exhaustive. Each specific diagnosis has it's own history, which should thus carefully be recorded (10). It is important to establish the mode of onset of the arthritis.

For instance the history of a patient being awakened by acute pain in the big toe is suggestive of gout. The sudden onset of pain when twisting the knee is suggests a mechanical cause.
The quality of pain must also be taken into account. Pain at rest and stiffness being suggestive of an inflammatory cause.

A number of other diagnostic features should also be taken into account for instance: other concommitant conditions like diarrhea, urethritis, a previous history of arthritis, family history and a reaction to drugs (12).

A wide range of conditions are capable of producing acute arthritis and are amenable to diagnosis. However, some remain difficult to diagnose. Fortunately these usually resolve spontaneously.

Septic arthritis is an urgent medical condition. A rapid diagnosis is particularly important in these cases. A delay of 24 hours may alter the prognosis significantly for the worse (6).

Micro-organisms usually reach the joint by haematogenous spread from a primary infection elsewhere; occasionally no source can be found (1,14).
An increased susceptibility to joint infection occurs in patients with diabetes, in those with lymphomas, and in those receiving corticosteroids or other immunosuppressive drugs. In addition, joints previously damaged by arthritis, such as rheumatoid arthritis or trauma, are more liable to infections (22,21).

Acute bacterial arthritis is caused by many different types of bacteria; the ones most commonly encountered are: *N.gonorrhoeae, S.aureus, S.pneumoniae, S.pyogenes, H.influenzae type B*, and other Gram-negative bacilli (*E.coli, Pseudomonas,* etc.) (32). Septic arthritis due to *Haemophilus influenzae type B* occurs mostly in children; gonococcal arthritis is a disease of sexually active adults. Joint sepsis with gram-negative bacilli tends to occur in patients with underlying infections of the urinary or digestive tract and in patients with impaired resistance to infection. Patients with salmonella arthritis often have evidence of underlying osteomyelitis (20,28). Infectious arthritis of the spine is seen in brucellosis, salmonella infections and tuberculosis (17). The onset of bacterial arthritis is usually abrupt and accompanied by fever and chills. One or more joints may be involved.
The affected joint is warm, erythematous, swollen and painful; however these signs may be masked in patients receiving corticosteroids.

Marked guarding of the joint and muscle spasms are common. The larger joints, such as hips, knees and shoulders are more commonly affected, and the wrists, ankles, elbows, sternoclavicular and sacroiliac joints less often (8,21).
In the early stages of infection the synovium is oedematous and infiltrated by neutrophils (2). An effusion with many neutrophils forms rapidly. Lysosomal proteolytic enzymes are released from neutrophils and destroy articular cartilage,

subchondral bone and joint capsule. Small abscesses appear in the synovium and subchondral bone, and necrotic debris collects in the joint space. During healing, proliferation of fibroblasts may lead to ankylosis (14).

Joint aspiration should be performed in any patient suspected of having a septic joint. The Gram stain frequently reveals microorganisms. Culture of the synovial fluid and blood should be performed even if the Gram stain is negative.
Radiographs of the joint, early in infection, show only a distention of joint capsule, but later X-rays reveal juxta-articular osteoporosis, joint space narrowing due to cartilage destruction and bony erosion of the articular surface (13).
The diagnosis of septic arthritis is confirmed by a positive culture from synovial fluid or tissue.

The acute arthritis of gout or pseudogout may be mistaken for septic arthritis because of the monoarticular involvement and manifestations of acute joint inflammation. They are easily distinguished by the finding of the characteristic crystals in synovial fluid. Other types of inflammatory arthritis, such as psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, or rheumatic fever, may also be confused with septic arthritis, especially when only one or few joints are involved (10).
In a patient with generalized arthritis (such as rheumatoid disease) who develops fever and chills and has one joint disproportionately more inflamed than other joints, the possibility of septic arthritis should be carefully ruled out by examination of the synovial fluid cells and by culture of synovial fluid.
Septic arthritis requires prompt treatment with appropriate antibiotics. Bactericidal levels of antibiotics can be achieved with systemic administration. Direct administration into the joint is not recommended and may in itself produce a chemical synovitis (23).

Aspiration of the joint once or several times a day should be performed to reduce the pressure in the joint and to remove pus that is generated by proteolytic enzymes. Open surgical drainage is usually not indicated except in septic arthritis of the hip or in a joint with chronic suppuration (26).
Splinting of the affected joint will make the patient more comfortable and reduce the degree of flexion deformity. Prolonged splinting, however, should be avoided since it may lead to permanent joint stiffness. When the inflammation has subsided, physical therapy will aid the recovery of normal joint function (35).
Nevertheless, with accurate and early diagnosis the prognosis for the vast majority of patients is excellent (27).

II.2.2. Chronic Arthritis

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, osteoarthritis and systemic lupus erythematosus (SLE) are all diseases that can be listed as forms of chronic arthritis (13). Reduced mobility, malnutrition, the presence of damaged joints, prostheses and drugtreatment, including non-steroidal anti-inflammatory drugs, all predispose the patient with chronic arthritis to infection (7).

In rheumatoid arthritis and SLE impaired host defence mechanisms associated with the disease (15) are present as well. The special features of rheumatoid arthritis will be discussed later.

Apart from these diseases there are also some forms of chronic arthritis that are caused by intra- or extra-articular microorganisms.

a. intra-articular micro-organisms

The most important causes of arthritis due to bacterial invasion of the joint are respectively: tuberculosis, brucellosis, Lyme disease and other spirochaetoses, *Streptobacillus moniliformis, Mycoplasmata* and as a special form: Whipple's disease (9) which is a multisystem disease characterized by arthritis, serositis, diarrhea, malabsorption, weight loss and lymphadenopathy.

b. extra-articular micro-organisms

This form of chronic arthritis is also called reactive arthritis. It is the result of an interaction between a susceptible human genotype and an organism. In simple terms: soil and seed results in arthritis. It is characterized by an interval of several days between the triggering infection and the onset of arthritic symptoms, negative synovial fluid culture and no response to antibiotic treatment.

Individuals with HLA B 27 are susceptible to developing arthritis after certain infections (4).

Four diseases of this type are not related to HLA B27: Rheumatic fever, meningococcal arthritis, gonococcal arthritis and intestinal bypass arthritis. The latter is an iatrogenic disease and follows surgery for gross obesity. The reactive arthritis forms related to HLA B27 are: EARA (enteric acquired reactive arthritis): *Shigella flexneri, salmonellae, Yersinia enterocolitica, Campylobacter jejuni* and SARA (sexually acquired reactive arthritis).

Most common forms of chronic arthritis such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and post-infective arthritis probably share basic processes in causation despite obvious differences between them in clinical features.

For most of this century specific infective agents that cause individual types of arthritis have been sought in synovial tissue and fluid; but, with few exceptions, the results have been discouraging (5).

The use of modern laboratory techniques and immunological concepts may lead to a new approach which might eventually elucidate the cause of arthritis.
In view of the subject of this thesis the importance should be stressed of the association between infection and arthritis and of the basic processes and relations that are found in the aetiopathogenesis of chronic arthritis.

It is well recognised that transient arthralgia is a common feature of many microbial and viral infections (11). An arthritogenic microorganism can produce arthritis by a number of different mechanisms depending on the portal of entry and the host response. With improving techniques specific infections causing subsets of arthritis may be discovered. However it seems unlikely that a single organism will prove to be responsible for many of the commoner heterogenous group of chronic arthropathies (9).

Nevertheless there may be a common denominator; it is possible that peptidoglycans found on the outer membrane of the bacteria are important in this respect (16,24).

Inflammation is related to cytokines which can directly affect infection (12,30) as well as control the cellular respons.

They also induce the acute phase response, important for clearing of damaged cells and micro-organisms (25). The HLA status is important in governing the host response and can dictate the clinical presentation (19). Regulation of the mucosal immune response, particularly the role of IgA, has been reported in rheumatic diseases (33,34). The ability to prevent bacteria becoming embedded in mucosal surfaces may be important and may not be immunologically based. Secretion of blood group antigens in the joint inhibits bacterial adherence and the ability of streptococci to adhere to mucosal surfaces is probably important in rheumatic fever (3). There is preliminary evidence that ankylosing spondylitis may be associated with ABO non-secretors (29). The broad spectrum of other host factors include: age, gender, control of arachidonic acid metabolism, acute phase response, complement, and humoral and cellular immunity (9).

II.3 References

1. Ainscow DAP, Denham RA. The risk of haematogenous infection in total joint replacements J Bone Joint Surg(Br) 1984;66:580-2.
2. Bird IN. Role of polymorphonuclear leukocytes in the pathogenesis of infective arthritis. in: Infections and arthritis.1989;Kluwer Academic Publishers.
3. Blackwell CC, Jonsdottir K, Hanson MF, et al. Non secretion of ABO bloodgroup antigens predisposing to infection by Haemophilus influenzae. Lancet 1986;2:687.
4. Brewerton DA, Caffrey M, Nicholls A, et al. Reiters disease and HLA-A27 Lancet 1973;2,996-8.
5. Brewerton DA. Causes of arthritis. Lancet 1988;1063-6.
6. Broy SB and Schmid FR. A comparison of medical drainage and surgical drainage in the initial treatment of infected joints. Clin Rheum Dis 1986;12:501-23.
7. Brun-Buisson CLJ, Saada M, Trunet P, et al. Haemolytic streptococcal gangrene and non-steroidal anti-inflammatory drugs. Br Med J 1985;290:1786.
8. Burer JHG, Groot A, Laar MAFJvd, et al. Bacteriele gewrichtsinfecties: een retrospectief onderzoek naar de infectiebron. Ned Tijdschr Geneeskd 1989;133(34):1693-6.
9. Dawes PT, Sheeran T. The relationship between bacteria, related organisms and chronic arthritis. in: Infections and arthritis. 1989; Kluwer Academic Publishers.
10. Does Evd. Arthritis-arthralgie. Huisarts en wetenschap 1988;31;(11):369-72.
11. Dudley Hart. Arthralgia. Ann Phys Med 1970;6:257-61.
12. Editorial Bacterial arthritis. Lancet 1986:721-2.
13. Gilliland BC, Mannik M. Infectious arthritis. in: Principles of internal medicine. 1974 McGraw-Hill Book Company New York.
14. Goldenberg DL, Reed JI. Bacterial arthritis. New Engl J Med 1985;312(12):764-71.
15. Harris Ed. Rheumatoid arthritis. Pathophysiology and implications for therapy. New Engl J Med 1990;322(18) :1277-89.
16. Heymer B, Schleifer KH, Read S, et al. Detection of antibodies to bacterial cell wall peptidoglycan in human sera. J Immunol 1976;117:23-6.
17. Hodinka L, Gomor B, Meretey K, et al. HLA-B27-associated spondylarthritis in chronic brucellosis. Lancet 1978;1:499.
18. Kelly PJ, Karlson AG. Muskeloskeletal tuberculosis. Proc Mayo Clin 1969;44:73.
19. Lambert M, Marion E, Coche E, et al. Campylobacter enteritis and erythema nodosum. Lancet 1982;1:1409.
20. Maki-Ikola O, Gransfors K. Salmonella-triggered reactive arthritis. The Lancet 1992;339:1096-8.
21. Manshady RH, Thompson GR, Weiss JJ. Septic arthritis in a general hospital 1966-77 J Rheumatol 1980;7:523-30.
22. Meijers KAE, Dijkmans, BAC Hermans J, et al. Non-gonococcal infectious arthritis: a retrospective study. J Infect 1987;14:13-20.
23. Nelson JD. The bacterial aetiology and antibiotic management of septic arthritis in infants. Pediatrics 1972;50:437-40.

24. Park H, Schumacher HR, Zeiger AR, et al. Antibodies to peptidoglycan in patients with spondyloarthritis: a clue to disease aetiology. Ann Rheum Dis 1984;43:725-28.
25. Pepys MB. C-reactive protein fifty years on. Lancet 1981;1:653-7.
26. Petersen S, Knudsen FU, Anderson EA, et al. Acute haematogenous osteomyelitis and septic arthritis in children. Acta Orthop Scand 1980;51:451-57.
27. Platt PN. The red hot joint-acute monoarthritis. in: Infections and arthritis.1989; Kluwer Academic Publishers.
28. Robbins SL. in: Pathology. joint and related structures. W.B.Saunders Company. 1967 London.
29. Schnebaum R, Blackwell CC, Forster PJG, et al. Non secretion of ABO blood group antigens: a host susceptibility factor in the spondyloarthropathies. Ecul Symp. Rome IGPI 1985;41.
30. Scuderi P, Sterling KE, Lam KS, et al. Raised serum levels of tumor necrosis factor in parasitic infections. Lancet 1986; 2:1364-5.
31. Shepard CC. Other mycobacterial infections. in: Principles of internal medicine. New York: McGraw-Hill 1974.
32. Soesbergen RM. Bacteriële artritis. Ned Tijdschr Geneeskd 1987;131(44):1953-5.
33. Stanworth DR. IgA dysfunction in rheumatoid arthritis. Immunol Today 1985;2:43-5.
34. Strober W, Richman LK, Elson CO. The regulation of gastrointestinal immune responses. Immunol Today 1981;2:156-61.
35. Walker DJ. Management of the septic joint. in: Infections and arthritis. 1989; Kluwer Academic Publishers.

III. Extrapulmonary tuberculosis

III.1. Etiology

Mycobacterium tuberculosis is a rod of 2 to 4 µm in length and 0.3 µm in thickness and is only one of a fairly large group of Gram-positive, acid-fast rods that includes both pathogenic and saprophytic organisms (33). Its distinguishing staining property, i.e., resistance to decolorization by acid alcohol when stained with basic fuchsin, is related to the waxy component of the cell wall, probably specifically to its content of mycolic acid. This acid-fast property is dependant in some way upon the structural integrity of the bacillus; it is lost when the organisms are damaged by grinding but is not affected by prolonged extraction with fat solvents.

Tubercle bacilli are strict aerobes and thrive best when there is a P_{O_2} of 100 mm Hg or more and a P_{CO_2} of about 40 mm Hg. The organs most commonly affected by tuberculosis are those with relatively high oxygen tension; metastatic foci are most common in the apices of the lungs where the P_{O_2} is in the range of 120 to 130 mm Hg in the upright position, followed by the kidney and the growing ends of the bones, where the P_{O_2} approaches 100 mm Hg (33). Two strains of *M. tuberculosis* complex affect man: human and bovine.

By far the greatest number of cases are caused by the human strain. Programs of elimination have until recently been very effective in the western world. Avian bacilli have little invasiveness for man. Several other species of socalled "atypical" mycobacteria have been noted to cause chronic infections. The most common are the avian Battey group (*Mycobacterium intracellulare)* and *Mycobacterium kansasii.* These atypical mycobacteria appear not transmissable in human (38). The subject of this thesis is restricted to human *M. tuberculosis.*

III.2. Immunology

After the first contact with mycobacteria there is only a mild local and systemic reaction, because there is no immune response. The lungs are usually the first site of the infection. Most mycobacteria ingested by macrophages are killed after phagocytosis and clinical disease does not occur. The bacteria may however survive intracellularly and multiply (7). Release of mycobacteria after lysis of these macrophages causes haematogenous and/or lymphogenous spread and bacteria may settle in any organ in these first weeks before specific immunity is provoked (40).

In this way cell-mediated immunity results. In this process many different cell types are involved : T-lymphocytes, T-helper cells, T-suppressor cells, alveolar macrophages which can be activated by lymphokines and body macrophages (2).
The host now develops a hypersensitivity to mycobacterial antigens. This process of hypersensitivity is influenced by age, sex and hereditary factors.
If the amount of antigen is high the hypersensitivity reaction itself causes tissue

destruction and celldeath; this is known as caseation. Liquefaction of a caseous lesion is the most harmfull response in this stage. Tubercle bacilli can also multiply extracellularly in this period and spread through the body (4).

III.3. Tuberculous arthritis

Tuberculous arthritis is a chronic destructive form of septic arthritis caused by *Mycobacterium tuberculosis*. Most patients have a detectable focus elsewhere in the body; however, in some patients no primary lesion can be detected (43).

Mycobacteria may settle for years in tissues, as so called dormant bacilli or persisters, before they cause disease (postprimary tuberculosis). Disease in bone and joint, however, may also affect adjacent tissues (40). On the other hand, miliary disease, as a result of haematogenous spread of mycobacteria may have its origin in a tuberculous bone lesion (40) (secondary miliary tuberculosis).

The bacilli infect the synovium either through the circulation or by extension from a tuberculous lesion in the adjacent bone. Tuberculous arthritis is more common in children but may occur at any age (5,12).

In general, tuberculosis of bones and joints is thought to be a postprimary manifestation of tuberculosis. The clinical disease may begin soon after or even many years later after primary infection (3,16,38,41).

This occurs when the balance between cellular immunity and mycobacteria is disturbed, for instance by certain drugs like corticosteroids and cytostatics, radiotherapy, intercurrent infection and other circumstances that diminish resistance e.g. alcoholism, malnutrition and stress. This process is known as endogenous reactivation.

Besides this phenomenon of endogenous reactivation there are literature references, mentioning the possibility of exogenous reinfection (20,31,34,36,38,42).

When tuberculous infections were much more prevalent in the Netherlands than they are now and before chest roentgenograms provided evidence of old foci, exogenous reinfection was widely thought to play an important part. Although declining tuberculosis rates make exogenous reinfection less likely in developed countries it has been described in several case reports (1,22,26,27). Moreover, it has long been suspected that exogenous reinfection is important in developing countries where tuberculosis is epidemic and where the immunity acquired by previous infection may be incomplete because of stress, malnutrition and concomitant disease (6,38).

pathology

The tuberculous process in the joint produces synovitis with the formation of a pannus of granulation tissue over the articular cartilage. The subchondral bone is

involved, and areas of necrosis occur. Destruction of articular cartilage occurs later in the course, followed by fibrous ankylosis (31).

Tuberculous arthritis has an insidious onset, is usually monarticular, and usually affects the spine, hips, and knees (21). The affected peripheral joint is swollen, warm, and tender and has a decreased range of motion. Erythema over the joint is minimal, and pain is usually a later manifestation.

The hypertrophied synovium gives the joint a boggy, doughy feeling. Muscle atrophy and spasm of the affected extremity occur. Tenosynovitis of the flexor tendon sheaths of the wrist may compress the median nerve and produce a carpal tunnel syndrome. Regional lymphadenopathy is usually present (31).

clinical stages

The patient may have only slight fever. Weight loss is common. The course of untreated disease is one of progressive joint destruction, but spontaneous remission sometimes occurs.
The tubercle bacilli may be seen on smears of synovial fluid but are more likely to be found on biopsy of synovial tissue or of regional lymph nodes (41).

In tuberculosis of bone and joints three clinical stages of disease can generally be distinguished (24,29).

Stage 1. Early onset. In the beginning the patient has only intermittent pain and a slight disability. At rest the pain subsides but later on may become more prominent . Movement is avoided. There is a mild temperature rise up to 38.5 °C. Because pain is not constant it may take weeks to months before medical advise is sought.

Stage 2. Active disease. Gradually the disease progresses resulting in an abscess. Pain becomes more severe and abscess formation exerts pressure on the surrounding tissues. Fever is up to 39-40 °C. The "cold" abscess differs from pyogenic abscesses in that it is less warm and red, less painful on pressure and it shows slow progression due to differences in growth rate.

Stage 3. Healing stage. If no treatment is started the patient may die of complications: miliary spread of mycobacteria, or secondary infections and subsequent septicemia. If however the infection is overcome without surgical or drug intervention, endogenous reactivation is still imminent. Without medical intervention some patients never reach this final stage but develop chronic disease. The patient may suffer from a chronic draining sinus which is often secondarily infected.

radiology

Radiological findings vary with the severity of the infection, the reaction of the individual and the stage of the disease. Clinical symptoms sometimes appear

before any radiological signs can be detected; there is a lag between the infection of the bone and the occurrence of sufficient decalcification to appear in a radiograph, particularly when small foci are developing in a deep-seated bone. Post-mortem findings have shown that a bone which appeared normal in the X-ray may be extensively infiltrated with tuberculous infection.

Radiographs of peripheral joints in early disease show capsular distension and juxta-articular osteoporosis. Bony erosions at the joint margin, subchondral bone destruction, and jointspace narrowing are observed later in the disease. Films of the spine show destruction of the vertebral body, vertebral collapse, and loss of intevertebral disk space (17,39,40).

history

The history of the patient will often help in establishing a diagnosis. Attention should be directed to the onset, the duration of symptoms, any loss of weight or energy, the occurrence of night cries, and the character of the pain, if any.

The history may reveal contact between the patient and a case of open tuberculosis.

It is characteristic for tuberculosis that the symptom which first insinuates itself upon the attention of the patients or their parents does so very gradually. The patient very seldom associates the beginning of his trouble with any particular day: if, for instance he says that his symptoms began on Tuesday the cause is probably not tuberculous (14).

Generally the first symptom noticed by the patient or parent is an interference with function and some swelling rather than pain. Indeed pain and tenderness are slight at first, the characteristic features being limitation of movement and a swollen warm somewhat tender joint with the enlargement due to swollen synovial membrane rather than to fluid.

The inquiry may have revealed: the likelihood of human infection, previous manifestations of tuberculosis, some loss of health and vigour and a history of an injury from six to twelve weeks previously with a normal joint during most of the interval (14).

clinical examination

The presence of a joint swelling without redness of the skin or much fluid in the joint, with little tenderness and only slight increase in warmth forms a clinical picture strongly suggestive of tuberculosis.
After making these observations one should try very gentle passive movements. Nothing is to be gained by attempts to force movements; and movements under anaesthesia are contra-indicated if tuberculosis is suspected, because the anaesthetic eliminates the protective muscular spasm. One may get a little information but at the risk of doing a good deal of harm.

The degree of pain on movement varies considerably. If the joint has rested for some days there may be deceptively little discomfort when the doctor handles it gently. But as a rule movement is severely limited by muscular spasm e.g. in the hip the pelvis moves with the limb. The characteristic sign of inflammation of a joint is this lack of movement or limitation by muscular resistance of movements in all directions.

The position of the joint should be carefully noted for at an early stage of inflammation a joint will often be held in in a characteristic position, that which most relieves the pain due to its distention by fluid. Later when the joint is completely disorganised the deformity will depend on habitual posture, on gravity and on the pull of the most powerful muscles.

III.4. Different manifestations of tuberculous arthritis

tuberculosis of the hip

There are variations in the manifestation of joint tuberculosis. The special features of tuberculosis of the hip are its tendency to affect children, the tendency to early bone destruction and the crippling nature of subsequent deformities.

The high incidence among children was referred to by Dobson (14) who reported that of a series of 320 patients 47.5 % were in the first decade. In this group only 9 patients (2.8%) showed no bony lesion. The nature of the joint offers a variety of deformity following destruction by disease and to these may be added gross shortenings of the limb due to premature fusion of the lower femoral epiphysis.

tuberculosis of the spine

Hippocrates reported a patient with spinal caries which was associated with paralysis of the lower limbs. This paralysis was reported to have recovered when a cold abscess presented on the patient's back. More than two thousand years later this report was brought to the attention of Percival Pott, surgeon to St. Bartholomew's Hospital by his friend Dr. Camaron of Worcester and Pott subsequently practised the treatment of this form of paraplegia by drainage of the paravertebral abscess (25). This form of disease has also been observed in Egyptian mummies (18).

Spinal tuberculosis may occur at any age. The greatest incidence is in the third decade and it is the least common in the elderly. The lesion may affect any part of the spinal column, but it is most commonly found in the lower thoracic and thoracolumbar regions, next most commonly in the lumbar spine and less commonly in the upper dorsal, cervical and lumbosacral regions.
The lesion is rarely isolated and where a single lesion can be seen it is almost always surrounded by minor lesions which are not visible so that a number of vertebrae above and below may be affected. An appreciation of this is important because it means that obliteration of an obvious lesion will not necessarily produce a complete cure.

The nature of the spinal tuberculous lesion is remarkably constant. One or more segments are involved but the pathological presentation may vary because of the anatomy of the blood supply.

Paraplegia is the most serious complication which can result from tuberculous disease of the spine. It used to develop in about 10 per cent of all cases of Pott's disease in all age groups, so that it was found most commonly in children and in adults up to the age of 25 years after which age the incidence falls.

This follows closely the incidence of Pott's disease itself in different age groups. The paraplegia results from interference with conduction in the spinal cord; interference with the cauda equina is extremely rare. Thus paraplegia is rarely seen when the disease is below the first lumbar vertebra. Its incidence again follows closely the incidence of the disease in the different regions so that the highest incidence is to be found in the lower thoracic region.

sacro-iliac tuberculosis

Tuberculosis of the sacro-iliac joint may be an associated lesion affecting one or rarely both sacro-iliac joints, or it may occur as one among several tuberculous lesions in the same patient. The disease occurs most commonly in young adult patients. The disease has the tendency to form sinuses. The lesion is usually situated in the subchondral bone of the sacro-iliac synchondrosis.

tuberculosis of the knee

The mode of onset, symptoms and physical signs of tuberculosis of the knee are similar to those which have already been described for other tuberculous joints. There are two features however especially associated with tuberculosis of the knee.

The first feature is the superficial nature of the joint which makes the physical signs easily demonstrable. Early on the soft tissue structures become oedematous and cause loss of the contours of the joint. The name which used to be given to a tuberculous knee was "tumor albus" and suggested the fusiform swelling. In the early stages there is an increase in the amount of synovial fluid present. The synovium is palpable round the joint and over the suprapatellar pouch. In many patients the disease may seem to be limited to the synovium, but it must be remembered that the origin is haematogenous and synovium and subchondral bone are infected together and that, in the majority of patients operated on, some evidence of subchondral bone disease is observed (14). The second feature especially associated with tuberculosis of the knee is the frequency with which it is associated with active pulmonary tuberculosis in young adults.

tuberculosis of the shoulder

Tuberculosis of the joints of the upper limb presents somewhat different problems from those of the lower limb. The lower limb joints are perhaps of more simple

structure, designed for weight bearing as well as locomotion and this relative simplicity perhaps makes restoration of anything approaching full function easier than in the more complicated shoulder and elbow joints. The wrist does not present the same difficulty.

Yet it has always been recognized that restoration of function of upper limb joints is of special importance as the patient depends on so many complicated movements of the arms and hands. Until the introduction of anti-tuberculous drugs the prospect of recovery of function of an tuberculous upper limb joint was poor and the generally accepted view was that the joint should be sacrificed by arthrodesis. In the treatment of tuberculosis of the shoulder and elbow recovery of function needs special attention.

Tuberculosis of the shoulder occurs less frequently than tuberculosis of other major joints but is not uncommon, the incidence being 1 per cent of all bone and joint tuberculosis.

tuberculosis of the elbow

The elbow is a composite joint. There is a common synovial membrane in these joints. The customary changes which affect all tuberculous joints are seen: synovitis, pannus formation, cartilage and bone absorption and the formation of cold abscesses. In many patients a cavity in the upper ulnar metaphysis is present from an early stage . The humerus is not an uncommon site for an osseous lesion. This may ulcerate into the joint and is frequently the source of cold abscess formation. Associated tuberculous lesions elsewhere in the body are common and were found in about 57 per cent.

tuberculosis of the wrist and hand

Tuberculosis of the wrist occurred in twelve patients of a series of 512 suffering from skeletal tuberculosis (14). Two of these twelve were children. Eight of the ten adult patients had overt tuberculous lesions elsewhere in the body, which was also a common finding in other peripheral joints with tuberculous arthritis. Tuberculosis of the wrist usually begins in the carpometacarpal joints, but this is not invariable and sometimes the only evidence to be seen is in an individual carpal bone. From the carpometacarpal joints the disease extends into the carpus until the radiocarpal joint is involved and the whole wrist may be disorganized. The carpal bones are prone to infection particularly in the elderly, when it is extremely chronic and often leads to widespread destruction with extensive sinus formation and secondary infection. The most manifest changes in the early stages are synovial, not only of the joints of the metacarpus, carpus and wrist, but also the tendon sheaths of the extensor tendons of the wrist. In contrast with the elbow joint which communicates with the superior radio-ulnar joint, the wrist joint does not communicate with the inferior radio-ulnar joint, because a triangular fibrocartilage forms a barrier. It follows that if treatment is started in the early stages the sequellae of the disease are less than in the elbow joint. If, however, the disease is already more progressed, considerable

destruction usually occurs with involvement of the lower ends of the radius and ulna in addition to the carpal bones. Abscesses and sinuses may frequently develop.

III.5. Diagnosis

Tuberculous arthritis is diagnosed by demonstration of mycobacteria in synovial fluid or tissue smear, histology, and/or culture. A positive culture is the only proof; a positive microscopic finding is very suspicious of tuberculosis. The tuberculin skin test is almost always positive. Apart from antimicrobial therapy surgical treatment may be necessary; this includes debridement, synovectomy, and joint fusion (41).

III.6. Treatment

There is no single method of treating tuberculosis of bone and joints. In general children heal better than adolescents, adults heal slowly and the elderly almost never achieve a final arrest. Therapy consist of a combination of antituberculous therapy, immobilisation, surgical intervention, general therapeutic measures and rehabilitation (40).

The aim of local treatment should be directed at the prevention and/or correction of deformity, the restoration of free movement whenever possible or if this is not possible to provide ankylosis in a stable position, to remove diseased tissue or tuberculous pus when necessary and to prevent secondary infection. These things must be done so that when treatment is complete the patients limb or spine is so well and truly healed that it will be permanently safe.

medicamentous therapy

The treatment of choice consist of the combination of isoniazid and rifampicin, supplemented by streptomycin and pyrazinamide during the first two months (intensive phase), followed by isoniazid and rifampicin in the continuation phase. (40). Drug therapy for tuberculosis is independant of localisation and age. Short course therapy in which pyrazinamide also plays an essential role is possible however only when isoniazid and rifampicin are used throughout the whole course. Short-course therapy (6-9 months) given under fully supervised conditions is very effective in the treatment of pulmonary tuberculosis. Studies on short-course therapy in extrapulmonary tuberculosis are promising (8,19).

Patients in communities in which there is even a small risk (> 2 percent) of single drugresistance should be treated with isoniazid, rifampicin, pyrazinamide, and ethambutol until the results of drug susceptibility testing are available. In certain areas of the city of New York, where many patients with tuberculosis are infected with strains resistant to two or more agents, at least five drugs are needed to protect against additional acquired resistance (13). For patients with HIV infection or AIDS in these areas, a six-drug regimen based on the local patterns of resistance may be indicated until the resistance pattern of the patient's organisms is known (15).

general measures

The healing of tuberculous disease of bone and joints is a longstanding problem for the patient. Certain general nursing measures are necessary with all patients. Optimal alimentation is important. The supine immobile patient must drink enough in order to avoid nephrolithiasis. Decubitus and contractures must be prevented. If stoolproblems exist the patient should be laxated. Adequate anticoagulant therapy is advised for the bedridden patient. Because of enzyme induction of the liver, rifampicin accelerates the breakdown of many medicaments, including anticoagulants.

immobilisation

There is no general agreement on the value and duration of immobilisation. Yet, it is an important measure in the treatment of tuberculosis of the bone and joints. Immobilisation creates the best opportunity for healing with the least sequelae. The aim of immobilisation is to create optimal circumstances for restoration of the bone in its original structure. Nevertheless this is not always possible, for instance when the patient is treated on an ambulatory basis. In those cases the risk of further destruction of bony tissue must be accepted (40).

corticosteroids

There is abundant clinical evidence to prove that the adrenocortical hormones decrease resistance to tuberculosis. Rees (28) described animal experiments which showed that tuberculous lesions were progressing more rapidly when cortison was administered. Also the report of the American Trudeau Society (1952) showed that in human beings tuberculous disease is aggravated by adrenocorticoid hormones. These early observations have subsequently been amply confirmed. Girdlestone et al. (14) have on several occasions found that in some cases patients suffering from rheumatoid arthritis harbour tubercle bacilli in joints which present all the clinical and microscopical characteristics of rheumatoid disease. Sometimes the patient on adrenocorticosteroid treatment for rheumatoid arthritis develops overt tuberculosis in the lungs or in a joint (14).

Especially in joint infection caused by *M.tuberculosis* the time between onset of symptoms and the diagnosis can be delayed (35). This in itself worsens the prognosis.

Septic arthritis is an infectious complication known to be overrepresented in RA. Intra-articular glucocorticosteroid injection is not infrequently complicated by septic arthritis within three months. Ostensson found in a matched controlled study a frequency of 1 case of septic arthritis per 2000 injections with steroids (23).

surgical therapy

The need for surgical therapy depends on the localization and extension of the bone lesion(s) and/or (cold) abscess. Surgery has a threefold purpose: (a) removal of sick tissue (pus, sequestrae, aseptic necrotic bone and devitalized discs or cartilage, (b) restoration of stability and (c) prevention of further deformities.

rehabilitation

Immobilisation often results in muscle loss. Contractures and bone deformaties give rise to abnormal function. Physiotherapy in active disease can do much harm and may intensify pain and make diseased bony tissue to collapse further. The healing stage with restoration of bony tissue and resorption of the abscess takes about 2 years after medicamentous treatment has started; so rehabilitation of a patient with bone and joint tuberculosis is a long lasting process.

III.7. References

1. Bates JH, Stead W, Rado TA. Phage typing of tubercle bacilli isolated from patients with two or more sites of organ involvement. Am Rev Respir Dis 1976;114:353-8.
2. Bates JH. Tuberculosis: susceptibility and resistance. Am Rev Respir Dis. 1982;125(3):20-25.
3. Burer JHG, Heijden AHMvd, Teertstra HJ, et al. Tuberculose van de schedel. Ned Tijdschr geneeskd 1986;130(4):169-72.
4. Collins FMR. The immunology of tuberculosis. Am Rev Respir Dis 1982;125(3):42-50.
5. Comstock GW. Epidemiology of tuberculosis. Am Rev Respir Dis 1982;125(3) 8-16.
6. ten Dam HG, Pio A. Pathogenesis of tuberculosis and effectiveness of BCG vaccination. Tubercle 1982;63:225-33.
7. Dannenberg AM. Pathogenesis of pulmonary tuberculosis. Am Rev Respir Dis 1982;125(2)23:25-29.
8. Dutt AK, Moers D, Stead WW. Short course chemotherapy for extrapulmonary tuberculosis. Ann Intern Med 1986;104:7-12.
9. Editorial. Interleukin-1 in deference of the host. Lancet 1985;2:536-7.
10. Editorial. Rheumatoid arthritis and tuberculosis. Lancet 1986:321-2.
11. Epstein FH. Rheumatoid arthritis Pathophysiology and implications for therapy. New Engl J Med 1990;322(18):1277-89.
12. Farer LS, Lowell AM, Meador MP. Extrapulmonary tuberculosis in the United States. Am J Epidemiol 1979;109:205-17.
13. Frieden TR, Sterling J, Pablos-Mendez A, et al. The emergence of drug-resistant tuberculosis in New York City. New Engl J Med 1993;328:521-6.
14. Girdlestone GR. Tuberculosis of bone and joint. 1965 Oxford University Press, Oxford.
15. Iseman MD. Treatment of multidrug-resistant tuberculosis. New Engl J Med 1993;329(11):784-91.
16. Karpman RR. Skeletal tuberculosis. Arizona Med J 183(3):169-70.
17. Linden AJvd. Osteo-articulaire tuberculose. Ned Tijdschr Geneeskd 1984;128(3):108-13.
18. Morse D, Brothwell DR, Ucko PJ. Tuberculosis in ancient Egypt. Am Rev Respir Dis 1964;90:524-41.
19. Medical Research Council Working party on tuberculosis of the spine: tenth report. Tubercle 1986;67:243-59.
20. Nardell E, McInnis B, Thomas B, et al. Exogenous reinfection with tuberculosis in a shelter for the homeless. New Engl J Med 1986;315(25):1570-5.
21. Newton P, Sharp J, Barnes KL. Bone and joint tuberculosis in Great Manchester 1969-79. Ann Rheum Dis 1982;41:1-6.
22. Ormerod P, Skinner C. Reinfection tuberculosis: two cases in a family of a patient with drug resistent disease. Thorax 1980;35:56-9.

23. Ostensson A, Geborek P. Septic arthritis as a non-surgical complication in Rheumatoid arthritis: relation to disease severity and therapy. Br J Rheum 1991;30:35-8.
24. Probst FP, Bjorksten B, Gustavson KH. Radiological aspects of chronic recurrent multifocal osteomyelitis. J Bone Joint Surg (Br) 1980;62: 376-80.
25. Pott P. Remarks on that kind of palsy of the lower limbs which is frequently found to accompany a curvature of the spine. Johnson 1779 London.
26. Raleigh JW, Wichelhausen R. Exogenous reinfection with mycobacterium tuberculosis confirmed by phagetyping. Am Rev Respir Dis 1073;108:639-42.
27. Raleigh JW, Wichelhausen RH, Rado TA, Bates JH. Evidence for infection with two distinct strains of Mycobacterium tuberculosis in pulmonary tuberculosis: report of 9 cases. Am Rev Respir Dis 1975;112:497-503.
28. Rees RJW. Brit Med Bull 1954;10:107.
29. Reinhard W. Die Tuberkulose der Knochen und Gelenke. 1966 Springer, Berlin Heidelberg New York.
30. Rich AR. The pathogenesis of tuberculosis. 2nd ed. Springfield, Ill.: Charles C Thomas 1951
31. Gilliland BC, Mannik M. Infectious arthritis in: Principles of internal medicine. 1974 McGraw-Hill Book Company New York.
32. Robbins SL. In: Pathology. Joint and related structures. W.B.Saunders Company. 1967 London.
33. Stead WW. Mycobacterial diseases. Tuberculosis. in: Robbins SL. Pathology. Mycobacteria. W.B.Saunders Company. 1967 London.
34. Romeyn JA. Exogenous reinfection in tuberculosis. Am Rev Respir Dis 1970;101:923-7.
35. Soria LM, Sole JMN, Sac AR. Infectious arthritis in patients with RA. Ann Rheum Dis 1992;51:402-3.
36. Stead WW. Pathogenesis of a first episode of chronic pulmonary tuberculosis in man: recrudescense of residuals of the primary infection or exogenous reinfection? Am Rev Respir Dis 1967;95:729-45.
37. Steensma J. Tuberculose van het skelet. Ned Tijdschr Geneeskd 1986;130(12):558-9.
38. Stead WW, Bates JH. Epidemiology and prevention of tuberculosis. In: Fishman A P ed. Pulmonary diseases and disorders New York: McGraw-Hill, 1980:1234-54.
39. Teertstra HJ, Taconis WK. Veranderingen in het röntgenbeeld van tuberculose van het skelet. Ned Tijdschr geneeskd 1986;130(4):157-62.
40. Thijn CJP, Steensma JT. Tuberculosis of the skeleton. Springer Verlag 1990 Berlijn.
41. Warns EHJ. Syllabus skelettuberculose. KNCV 1979 The Hague.
42. Ziegler JE, Edwards ML, Smith DW. Exogenous reinfection in experimental airborne tuberculosis. Tubercle 1985;66:121-8.
43. Kelly PJ, Karlson AG. Musceloskeletal tuberculosis. Proc Mayo Clin 1969;44:73.

IV. Rheumatoid arthritis and tuberculosis

IV.1. Introduction

In this chapter different aspects of rheumatoid arthritis will be discussed in relation to tuberculosis and the results of some relevant experiments will be given. This results in a theoretical model of the reaction of patients with rheumatoid arthritis if they are at the same time (re)infected with *M.tuberculosis*.

IV.2 Poncet's disease

Poncet described a form of polyarthritis in patients suffering from tuberculosis that was not caused by tuberculous infection of the joints (80). Various mechanisms have been suggested, the most popular being an allergic phenomenon affecting the joints (50). Although cases of polyarthritis have been described in patients with tuberculosis who have a undulating pyrexia and are systemically ill (2,42), controversy remains as to whether Poncet's disease exists as an entity (93). Insight into the possible immunopathogenesis of Poncet's disease is gained by examining an animal model of *M.tuberculosis*-induced adjuvant arthritis (AA) (10,75). In this model a chronic synovitis which histopathologically closely resembles rheumatoid arthritis is induced by injection of heat-killed and dissicated *M.tuberculosis* in oil-complete Freund's adjuvant (CFA). Intra-articular injection of various antigens alone without prior injection of CFA only leads to a transient synovitis that is not perpetuating. The model of AA will be discussed in more detail at the end of this chapter.
These data lead to an increase in the interest in the relation between tuberculosis and rheumatoid arthritis. From an epidemiological point of view this relation has been questioned because of lack of association in areas in which both the prevalence of tuberculosis and rheumatoid factor is high (72).

IV.3. Rheumatoid arthritis

symtomatology

Rheumatoid arthritis is a disease that gradually becomes symptomatic (51), beginning in the metacarpo-phalangeal joints (MIP), proximal interphalangeal joints (PIP) and wrists. The hip and ankles are rarely affected in the early stages of rheumatoid arthritis (37). General fatigue and malaise may be present before the joint symptoms and are probably generated by cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1) (45). Morning stiffness, a sensitive but nonspecific symptom of rheumatoid arthritis, is generated by an increase in extracellular fluid in and around the joint (45). As stated in Chapter II, joints in RA are more susceptible to bacterial infection (68,69,104) and this is a well recognised complication. In the case of *M. tuberculosis* as causative agent a delay in diagnosis and treatment is often observed (104).

epidemiology

Rheumatoid arthritis affects about 1 percent of the population worldwide. The overall prevalence of RA in the Netherlands is 1-2 percent (35). Women are affected more frequently than men at a ratio of 2:1 in younger patients. In patients with disease onset after the age of 60 RA is more equally distributed over both sexes. Because of its chronicity RA is a major problem in the elderly: 1,5% of the men and 4.7% of the women in the Netherlands over the age of 65 are suffering from RA (35). Unlike Lyme arthritis, no clustering of rheumatoid arthritis is reported. Indeed in familial clusters in which a shared environmental factor might be expected to play a role, the calender year of onset of the disease in affected twins agreed no more often than in matched pairs of sporadic cases (84). No geographically defined population exists with an exceptionally high incidence of the disease, although some differences between population groups are reported. Rheumatoid arthritis is rare in rural South African black people as compared with urban dwellers (6,89). Urbanisation may therefore be a riskfactor.

Population based studies of cases in both the United States (65) and the United Kingdom (87) support a decline in incidence in the past 25 years. These observations are compatible with several explanations such as, for instance, a change in diagnostic practice. It has also been suggested that oral contraceptives are in some way or another responsible for a decline in incidence (94).

Others have suggested that temporal patterns of rheumatoid arthritis are consistent with a similar cyclic change in the epidemicity and virulence of a specific, but as yet unknown micro-organism (19).

stages

It is essential to determine the pathobiological phase of RA. In stage 1 the presentation of a relevant antigen to an immunogenetically susceptible host is believed to trigger rheumatoid arthritis (45). More is known about immunogenetic susceptibility than about possible causative agents (67). The second and third stages of RA are similar in nature and differ only in their severity and amplitude. The immune response becomes located and organised in the perivascular areas in the synovial membrane. At the same time, the increase in the number of T-cells leads to the proliferation and differentiation of B-cells and to the production of antibodies within the expanding scaffold of new blood vessels and synovial-cell proliferation (56) (figure V.1a.) This eventually leads to irreversible destruction of cartilage typical of stage 4 (figure V.1b). This begins when the proliferating synovial membrane becomes organised in an invasive front that invades cartilage, tendons and subchondral bone. In stage 5 irreversible destruction is well under way and is almost complete. Attempts to protect joints from progressive destruction are unsuccessful (45).

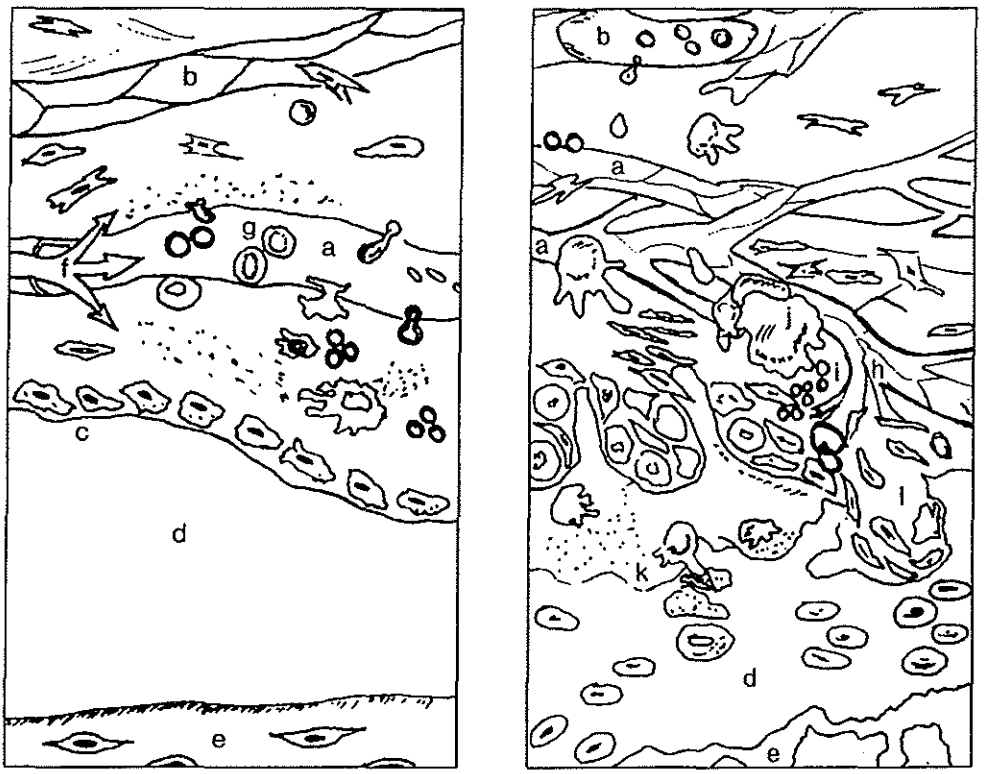

Figure IV.1a. stage I/II (left) and Figure IV.1b. stage IV (right) in RA. a.capillary b.lymphatic vessel c.synovial lining cells d. joint space e. articular cartilage f.unidentified etiologic agent carried to the joint g. sensitized lymphocytes are delivered by the blood h. ingrowth of blood vessels i.lymphoid follicles j. macrophages accumulate k. articular cartilage degrades l. ingrowth of pannus.

diagnosis

A careful clinical history and a thorough physical examination are essential for the diagnosis of rheumatoid arthritis. The most frequent differential diagnoses include other connective tissue diseases such as SLE, scleroderma and dermatomyositis. The criteria for diagnosis were revised by the American Rheumatism Association in 1987 (4). The following criteria are useful as guidelines for the diagnosis: morning stiffness in and around joints lasting at least one hour before maximal improvement is noted; swelling of the soft tissue (arthritis) observed by a physician around three or more joints; swelling of the PIP, MIP or wrist joints; symmetrical arthritis; subcutaneous nodules; a positive test for rheumatoid factor and radiological evidence of erosions, periarticular osteopenia or both in the joints of the hand, wrist or both. For the diagnosis at least four symptoms must have been present for six or more weeks.

IV.4. Possible primary causes

various infectious agents

The cause of RA is unknown. Current research is focusing on exogenous infectious candidates and endogenous substances such as connective-tissue proteins and altered immunoglobulins.

Many possible infectious candidates have been reviewed in detail by Philips (76) and Venables (95). HTLV 1, rubella virus, cytomegalovirus, herpesvirus and mycoplasmata have been proposed but none have received sustained scientific support.

In the past years there has been a resurgence of interest in the relation of Epstein-Barr virus to rheumatoid arthritis through the mimicry between EB-viral glycoproteins and susceptible sequences in the ß chain of HLA-Dw4, HLA-Dw14 and HLA DR1 Class II MHC molecules (82). Patients with serological evidence of a previous infection with Epstein-Barr virus have been shown to have serum antibodies that recognized the same peptides from both gp110 and HLA-Dw4 (83).

Parvoviruses have also been suggested as aetiological agents. Only two patients are known with early rheumatoid arthritis and evidence of a recent infection with parvovirus B19 (98). In two other patients tests for rheumatoid arthritis were transiently positive after a serologically well documented acute infection with parvovirus B19 (28).

Another hypothesis states that products of the bacterial load from the bowel lumen is the initiating factor in RA and not merely a single microorganism. In that case the microbacterial load as a whole has to be responsible, taking into account that the microbial components must be present in sufficient amounts (7). A bacterial component common to all bacteria, i.e. the bacterial cell wall peptidoglycan, is a serious candidate for causing joint inflammation symptoms. The permanent exposure of the immune system to these bowel derived antigens may account for chronicity of the disease. Clinical associations between arthritis and bowel inflammation or infection together with findings in some animal models support this hypothesis (86).

mycobacteria

The relation of mycobacteria to rheumatoid arthritis is also enjoying a resurgence of interest because these bacteria express heat-shock proteins (HSP's) which are the arthitogenic factors of adjuvant arthritis in rats (32).

Heat-shock proteins are produced in cellular organisms after sudden rises of temperature. In addition many other stressfull events elicit production of HSP's. Patients with rheumatoid arthritis have elevated levels of antibodies to heat-shock proteins from recombinant mycobacteria (92). Heat-shockproteins appear on cell surfaces in response to various kinds of stress. Animal and bacterial heat-shock proteins have much homology with human heat-shock proteins and are believed to play a role in inflammation (79). Increasing evidence from experimental animal studies indicate that HSP's play a role in chronic arthritis (27). HSP's are immunodominant antigens of infectious organisms, including those bacteria that have been associated epidemiologically with chronic arthritis (73,100) such as *Borrelia burgdorferi, Salmonella, Yersinia, Campylobacter* and *Chlamydia spp.* (1,55).

HSP's are remarkably stable, as would be expected in view of their critical roles in the maintenance of cellular integrity (44). Striking is the extreme conservation of both amino-acid sequence and function in a given HSP family (66). Comparison of the primary structure of HSP's of different species shows regions of complete amino acid sequence identity (conserved identity) as well as regions that have a species specific sequence (non-conserved sequences). Thus, every microbial HSP contains a number of epitopes that are shared with those of human HSP's.
Infection entails stress for the micro-organism and the host resulting in an increased synthesis and expression of HSP's by the microorganism and the human host as well. During an active immune response directed against the microorganism the immune system must distinguish effectively between foreign epitopes of microbial HSP's and epitopes present on endogenous HSP's. When cells of the immune system select epitopes which are cross-reactive or identical to epitopes of self-HSP autoreactivity to endogenous HSP ultimately will develop.

A scenario leading to auto-immunity can therefore be described as follows: the encounter of infectious organisms (e.g. bacteria or parasites) results in the induction of a strong immune response to HSP's, including the activation of lymphocytes that recognize epitopes that are also present within the corresponding self-antigen -for instance- in the joint. Alternatively, infection with viruses (which do not carry HSP's by themselves) can lead to a chronic inflammatory response and local overproduction of self-HSP's in the joint. In both cases this may result in the processing by antigen presenting cells and subsequently recognition of HSP by T-cells. Once the process has been started it may be fuelled by overexpression of HSP's resulting from local effector mechanisms in the joint like (neuro) cytokines and degradative enzymes. Ultimately, both scenario's result in synovial inflammation and proliferation (41).

Data from animal experiments performed by Van den Broek et al. (15) and others (31) also provide suggestive evidence for a mechanism of this type in the pathogenesis of arthritis. Van den Broek used the streptococcal cell wall model (SCW): a single intraperitoneal injection of a sterile aqueous suspension of cell walls from group A streptococci induces a self-limiting acute polyarthritis and systemic illness followed by a chronic erosive polyarthritis. The chronic phase of the disease can only be induced in a susceptible rat strain (female Lewis rat), while in most rat strains tested in this model the acute disease can be induced. Joint inflammation develops coincidently with the deposition of cell wall fragments and the chronic phase is dependent upon the continued presence of cell walls in the joint. This does not explain the localization of the disease however, because cell walls can be demonstrated throughout the body.
Despite numerous studies on various features in this model, the exact pathogenic mechanism of this chronic joint inflammation is still not completely understood (17).

If an individual suffers from a (subclinical) bacterial infection, he will mount an anti-bacterial immune response in defence. As the data from Van den Broek make clear this anti-bacterial response can display an autoimmune character by reacting with

various cartilage components both at a cellular and at a humoral level. This cross-reacting response will in all probability need some aberrant conditions (defective suppression, joint trauma or suppressor/feedback mechanism (18)) to come to full expression and give rise to joint lesions. The preferential presence of bacterial-primed mononoclear cells in the joints can be explained because cross-reactive antigenic material is amply available in the form of cartilage or in later stages degradation products thereof (14).
Dose response studies in SCW primed mice that were challenged intravenously with SCW amounts too small to induce a primary arthritis were able to reactivate a chronic arthritis, suggesting that an inflamed joint is in a hyperactive state, probably due to locally retained lymphocytes (15).

Not all bacteria are able to induce an arthritis when administered in mineral oil (57,58). AA induced by bacterial CWF from the indigenous human flora has not been reported until recently. Severijnen et al. have reported that *Eubacterium aerofagiens* CWF ground in IFA induced a chronic persistent arthritis after s.c. inoculation in the tail base of Lewis rats (85).
PG has found to be the arthropathic cell wall compound (59). The minimal PG structure with arthropathic properties when administered in IFA is the muramylpeptide (MDP) N-acetylmuramyl-L-alanyl-D isoglutamine, a cell wall component of almost all bacteria. The arthropathic activity of MDP depends on the mineral oil used and the amino acids coupled to the muramic acid: its stereo-isomer N-acetylmuramyl-D-alanyl-D isoglutamine does not induce arthritis (26).

Van den Broek et al. also showed that a response induced by one bacterial species can be reactivated by another non-related species or even by small common bacterial components like LPS (a cell wall structure of Gram-negative bacteria) and MDP. The latter may have important consequences for the maintenance of the arthritis: once an anti-bacterial response-and thus an anti-cartilage response- is induced by one bacterium, any other invading species or its degradation products is able to reactivate not only the anti-bacterial but also the anti-cartilage response. These reactivations of the anti-cartilage response by (subclinical) infections with bacteria from the environment or the individual itself e.g. from the gastrointestinal tract can give rise to (subclinical) exacerbations of the inflammation. Exacerbations could also be mediated by auto-antigen, released as a result of cartilage damage. Repeated reactivations of the arthritis can thus lead to chronicity. Because pre-treatment of mice with antilymphocyte serum (ALS) or haplotype-specific monoclonal anti-I-A antibodies completely suppresses the reactivation reaction it is likely that the above mentioned hyperreactivity is caused by antigen-specific T-cells which are retained in the inflamed joint (12,15,64).

An important question which has remained unanswered is why the disease resulting from intraperitoneal SCW injection manifests itself mainly as an arthritis, while the stimulus is present throughout the whole body in the form of SCW. One explanation might be that some bacterial components show some structural homology

with cartilage, and that this homology is responsible for an automimmune anti-cartilage response induced by bacteria besides the normal anti-bacterial response, thus directing the disease to the joints. There are several observations supporting this hypothesis: the *M. tuberculosis* specific T-cell clones A2b and A2c respond to cartilage proteoglycans (31,32), T-cells isolated from synovial fluid of a patient with M.Crohn associated with severe arthritis react to *Escherichia coli*, Bacillus-species, *S. pyogenes* and to cartilage proteoglycans (18). In addition, recent studies show that immunization of mice or Lewis rats with *S.pyogenes* or *E.coli* results in a cellular and humoral immune response against both Gram-positive and Gram-negative bacteria and various antigens from cartilaginous origin (14).
There is evidence supporting the existence of humoral cross-reactivity: post-streptococcal glomerulonephritis sera contain antibodies against glomural basement membrane (GBM) proteoglycans (36) and murine monoclonal anti-streptococcal antibodies react with GBM in vivo and in vitro (38,39). Finally, in sera from patients with various rheumatic diseases such as juvenile onset ankylosing spondylitis, pauciarticular juvenile arthritis and RA, antibodies to bacterial peptidoglycans which presumably cross-react with cartilage have been demonstrated (21,53), again suggesting a causal relationship between bacteria and arthritis.
Severijnen et al. (86) suggest that the composition of the oligopeptide side chain of PG is an important factor in determining arthropathic properties.

It is of particular interest that in synovial fluid from patients with rheumatoid arthritis there are relatively large numbers of "double negative" T-lymfocytes (lymfocytes without CD4 or CD8 surfacemarkers) with a distinct CD3-associated T-cell receptor composed of δ and γ chains. These cells proliferate in response to mycobacterial antigens (49). A broad range of inferences may be drawn from these and similar data: at the one end of the spectrum, the expression of heat-shock proteins could be merely an acute-phase reaction; at the other extreme the proliferation of T-cell receptor / heterodimers in response to mycobacterial antigens could be amplified and perpetuated by cross-reactivity with heat-shock proteins on synovial cells and therefore directly be related to the genesis of rheumatoid arthritis (45).

autoimmunity

Tolerance to "self" antigens is induced immediately after birth and the state of tolerance seems to be maintained by suppressor T-cells (91). That immunological tolerance might be an explanation for the inability to induce bacterial arthritides in most rat strains stems from the observation (60) that conventional F344 rats are known to be resistant to AA in addition to SCW, and -if the postulates of Van den Broek are valid- have thus become tolerant to certain "dangerous" bacterial epitopes. One would therefore expect F344 rats that have never encountered bacteria in their life not to be tolerant and thus susceptible to bacterial arthritis. Indeed, germ free F344 rats develop AA which is comparable with respect to chronicity and severity to that in susceptible Lewis rats (15). This observation suggests an important role for endogenous (gut flora) bacteria in the induction of tolerance and protection against autoimmune arthritis. The involvement of gut bacteria in the regulation of auto-

immunity is further supported by the finding that repopulation of germfree F344 rats with *E.coli* (oral administration) several weeks before arthritis induction makes F344 rats resistant to AA again (15).

Similar results have been found by Severijnen et al. (86). In addition they studied the anaerobic flora in RA. The flora of 10 RA patients contained significantly more anaerobic coccoid rods than the flora of 10 healthy individuals. The impact of this observation is not clear; an altered intestinal flora might be an expression of a genetic predisposition to RA. Severijnen concludes that the intestinal flora of healthy individuals and patients with RA harbour anaerobic bacteria with a wide range of arthropathic properties in the rat.

It can be concluded there is little difference of opinion among most investigators that autoimmunity plays a major role in the progression of rheumatoid arthritis; however data supporting autoimmunity as the initial cause of rheumatoid arthritis are less firm. Collagen and IgG are the endogenous proteins most often implicated in these hypotheses (27).

IV.5. Immunology

Antigen-presenting cells (macrophages or dendritic cells in the synovial membrane) are the first to be involved in a human immune response. They ingest, process and present foreign protein antigens to T-lymfocytes which initiate a cellular immune response and stimulate the differentiation of B-lymfocytes into plasma cells that secrete antibody.
Like dendritic cells, macrophages also have an antigen presenting function.
Rheumatoid synovial macrophages show upregulated expression of the adhesion proteins p150/95 and to a lesser extent CR3, compared with the osteoarthritic synovium (3). These molecules are important determinants of cell migration to sites of inflammation and may also play a role in perpetuation of the process. Synovial monocyte-macrophages therefore have the phenotype of activated or differentiated macrophages.
The relevant receptors on antigen-presenting cells are the Class II major histocompatibility-complex (MCH) molecules. Processed antigen binds to the MCH glycoproteins and is then recognized by the MCH-antigen complex.
Because there are few HLA molecules and an almost infinite number of antigens, the groove on each type of HLA molecule such as B27 or DR4 must be capable of binding several thousand different peptides. It is the T-lymphocyte receptors that provide the specificity of the response. Studies of the molecules of B27 and DR4 indicate that particular epitopes on the lips of the groove are strongly associated with ankylosing spondylitis and rheumatoid arthritis (11,43)
In rheumatoid arthritis the Class II MCH locus is associated with susceptibility.
A majority of patients with rheumatoid arthritis carry HLA (the human MHC)-DR4, HLA-DR1 or both (67). There is no significant association between rheumatoid arthritis and the Class I MCH, but it is important to emphasize that HLA-DR4 and

HLA-DR1 are not the only genetic components of susceptibility to the disease. It is also observed that HLA-DR4 is associated with a high responsiveness to antigens specific to M. tuberculosis, but not to antigens shared with other mycobacteria (74). Many data support the concept that shared or mobile epitopes that appear in different Class II molecules (probably as a result of gene-conversion events) determine susceptibility to the disease (71). There is growing support for the hypothesis that HLA-DR4 in addition to programming susceptibility to rheumatoid arthritis is related to the severity of the disease as well (22).

In association with class II antigens, presentation of immunogenic peptides to T-cells leads to activation of these cells and subsequent release of lymphokines, e.g. Il-2, IFN- etc. (5). This may induce the MHC class II expression on other cell types such as endothelial cells and fibroblasts which then also attain accessory functions and aid in sustaining the initiated immune response (5). In this respect the role of type A synovial lining cells is of importance. This subset of synovial lining cells contains macrophage like cells and express MHC class II antigens (20). They may therefore be able to sustain the immune response in addition to their classical role in phagocytosis of antigens.

In addition results of animal experiments suggest that mast cells contribute to cartilage damage and may play an enhancing role in the flare reaction of arthritis in mice (16).
In the rheumatoid synovial membrane a predominance of CD4 positive T-cells (helper induce phenotype) has been described (30,70) whereas the number of CD8 positive T-cells (suppressor cytotoxic phenotype) is low. Goto et al. (40) have shown that in the synovial fluid especially the suppressor phenotype (Leu 8+,Leu 15+) is decreased whereas the cytotoxic phenotype is relatively increased (Leu 8+,Leu 15-). The decrease of CD8 positive T-cells with suppressor function and the functional aberrations in this subset might explain the strong response of synovial fluid T-lymphocytes to recall antigens (63). On the other hand synovial fluid T-cells responded poorly to allo-antigens in a primary mixed leukocyte reaction (88) possibly due to CD4 positive suppressor T-cells (54). The same phenomenon has been observed by Pirzer et al. (77) in intestinal T-lymphocytes of patients with Crohn's disease. T-cells of normal mucosa are unresponsive to microbial and recall antigens in vitro. By stimulation in vitro with a range of microbial antigens the T-cells remain unresponsive whereas those from an inflamed mucosa had a proliferative response, suggesting that the unresponsiveness is abrogated in the inflammatory lesions. Infiltrating T-cells may therefore mediate chronic inflammation on encountering the many antigens present in the intestine.

The reaction of T-lymphocytes of RA patients to *M. tuberculosis* differs with the duration of the RA (48). In the first year of disease T-lymphocyte reactivity was increased in the synovial exudates of the affected joints but not in the peripheral blood. In patients with a disease duration of 1-10 years high reactivity in peripheral blood is found. In patients with a disease duration of more than 10 years lymphocyte reactivity did not differ from that in healthy controls.

homing of lymfocytes to the synovial membrane

In the early stages of rheumatoid arthritis, coincident with the neovascularisation of the synovial membrane, circulating lymfocytes adhere to the endothelium in postcapillary synovial venules that are marked by endothelial cells with particularly high walls. After adherence, the lymfocytes migrate through the walls of the blood vessels and aggregate in the characteristic micro-environment around the blood vessels below the synovial surface (24,29). Certain cytokines that are essential to the mediation of rheumatoid inflammation (e.g. IFN (101), IL-1 (23) and TNF (25)) enhance the adhesiveness of endothelial cells for lymfocytes. The proteins on the post capillary venules that encourage adhesion are referred to as vascular addressins; the cell-surface structures on the lymfocytes mediating recognition and adherence to the activated endothelium in the postcapillary venules are called "homing" receptors. Binding to postcapillary venules is organ specific. The structure of addressins from postcapillary venules in rheumatoid synovial membrane differs from that of addressins in lymfnodes or the gut (52,78) and these addressins may attract specific subpopulations of T-lymfocytes to the incipient synovitis in patients with rheumatoid arthritis.

cytokines

The role of cytokines is becoming more and more clear. Cytokines are small proteins that are produced by immunocytes, macrophages and fibroblasts and that affect gene expression in cells with cytokine receptors in a micro-environment such as those found in rheumatoid synovitis. They regulate the amplitude and the duration of the immune-inflammatory responses. As pointed out by Krane et al. the cytokines and their activities are complex (62); one cytokine may stimulate the proliferation of cells under some conditions and inhibit growth under others. The general unifying concept is that substances released by macrophages inhibit the expression of cytokines by lymfocytes in rheumatoid arthritis (81). The production of the cytokines IL-1 and TNF decrease with age (9). It is postulated by Harris that a yet unidentified cytokine with the specific ability to increase the proliferation and activation of helper-inducer T-cells, but not the other subset of lymfocytes, is produced in the rheumatoid lesion. He also suggests that factors derived from monocytes and macrophages may effectively suppress the expression of cytokines by the majority of T-lymfocytes (45).

IV.6. Experiments of interest concerning the relation between RA and Tuberculosis

Adjuvant arthritis

Adjuvant arthritis (AA) was first described by Pearson in 1956 (75). AA can be induced in susceptible strains of rats, e.g. Lewis rats, by heat-killed mycobacteria in oil (CFA) injected intradermally at the base of the tail or into the foot pad.

AA resembles rheumatoid arthritis in many aspects but there are also notable differences (61). The model is widely used because of its reproducibility. The disease is characterized by inflammation of the synovium, formation of pannus, destruction of cartilage and erosion of bone. The inflammation becomes manifest at about 12-14 days after infection and is prominent in the small joints of the extremities. After 30-40 days the inflammation subsides, but deformation of the paws may still be found. Clinically important drugs for management of chronic arthritis in humans such as non-steroidal anti-inflammatory drugs, corticosteroids, methotrexate and cyclosporin A inhibit this experimental auto-immune arthritis (97). AA has been shown to be a T-cell-mediated disease, because AA can be transferred into naive recipients with T-cells obtained from *M. tuberculosis*-immunized donors. The T-cell line A2 was found to induce arthritis in irradiated Lewis rats (46) (Figure IV.2). However, subclones of line A2 were found either to induce arthritis (clone A2b) or to prevent or therapeutically reduce AA (clone A2c or attenuated clone A2b)(47). This latter phenomenon suggests possibilities for T-cell "vaccination". Clones A2b and A2c proliferate in vitro and mediate delayed type hypersensitivity in vivo to *M. tuberculosis* as well as to a component of cartilage proteoglycans. These results have led to the hypothesis that molecular mimicry between *M. tuberculosis* and a cartilage component could be the cause of arthritis (33) (Figure IV.3.).
When proteoglycans were administered prior to *M. tuberculosis* a significant increase of incidence and severity was observed (96).
With the T-cell clones A2b and A2c it became possible to define the mycobacterial antigen and epitope responsible for AA. The crucial antigen was shown to be the mycobacterial HSP60 (32). By testing deletion mutants of the mycobacterial HSP60 it was demonstrated that the epitope recognized by A2b and A2c clone was identical: the nonapeptide 180-188 of mycobacterial HSP60 (32). Later on the heptapeptide 180-186 was shown to be the critical epitope (102). Recently it was found that these clones A2b and A2c both use the same ß T-cell receptor (TCR) (34). AA is also used as a model to study immunomodulation. Very critical in these experiments is the time at which the modulating agent is given. Pre-treatment with mycobacteria in saline or oil, mycobacterial HSP60 in oil or Incomplete Freund's Adjuvant (IFA) and the nonapeptide 180-188 in oil intradermally or intraperitoneally injected result in prevention and/or suppression of AA (99). Oral administration of mycobacteria has no effect on the outcome of AA (103).

trauma and cross-reactiveness

To test the hypothesis that a damaged joint together with a cross-reactive anti-SCW response are sufficient for a (transient) arthritis, Van den Broek et al. (15) immunized Lewis and F344 rats with SCW or with a control antigen (ovalbumin, OVA) and damaged the cartilage 21 days thereafter by i.a. injection of papain. Injection of papain was shown to result in a loss of 50 % of the proteoglycans within 24 hours. Indeed preliminary data showed that in Lewis rats which were immunized with SCW a monoarthritis occurred, while in Lewis rats immunized with OVA or in both groups of F344 rats no inflammation could be detected. Thus, a damaged joint together with a cross-reactive anti-bacterial response could be sufficient to induce arthritis (Figure IV.4).

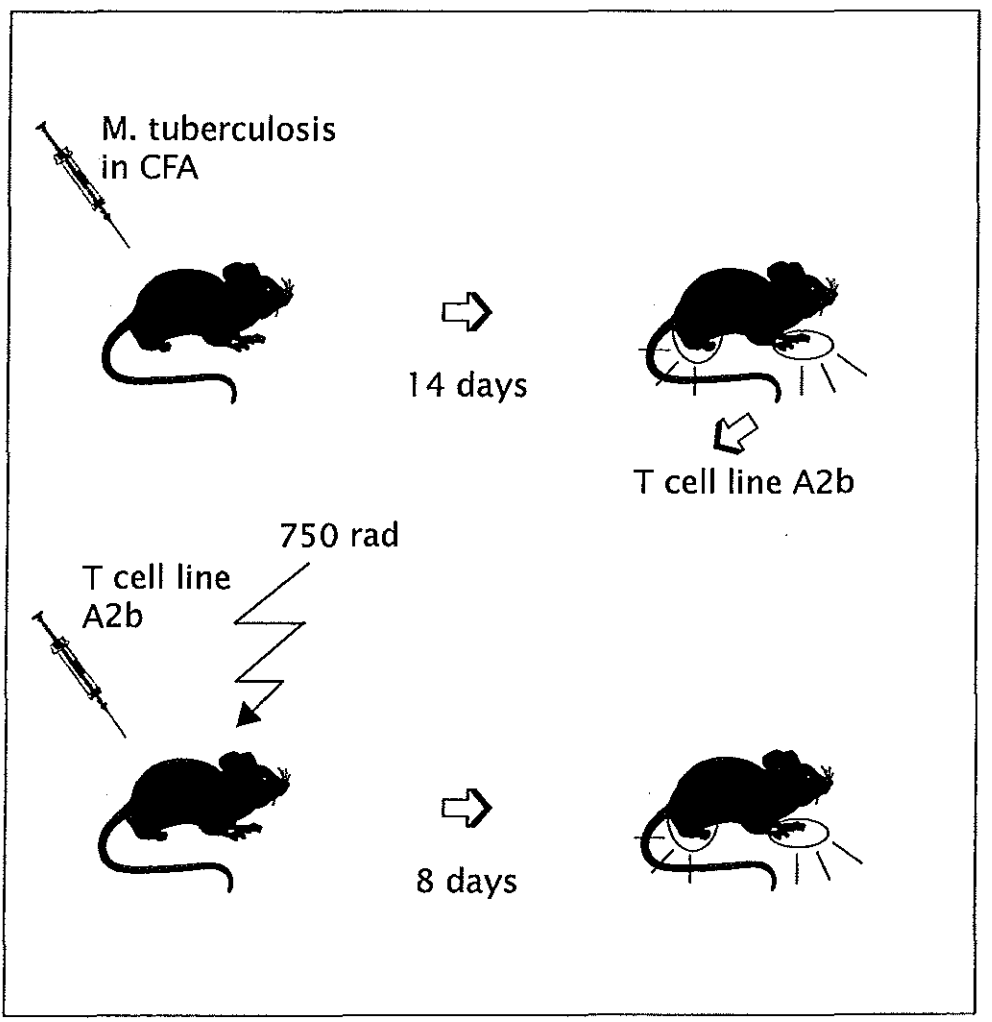

Figure IV.2. Schematic representation of the adjuvant arthritis model (AA).

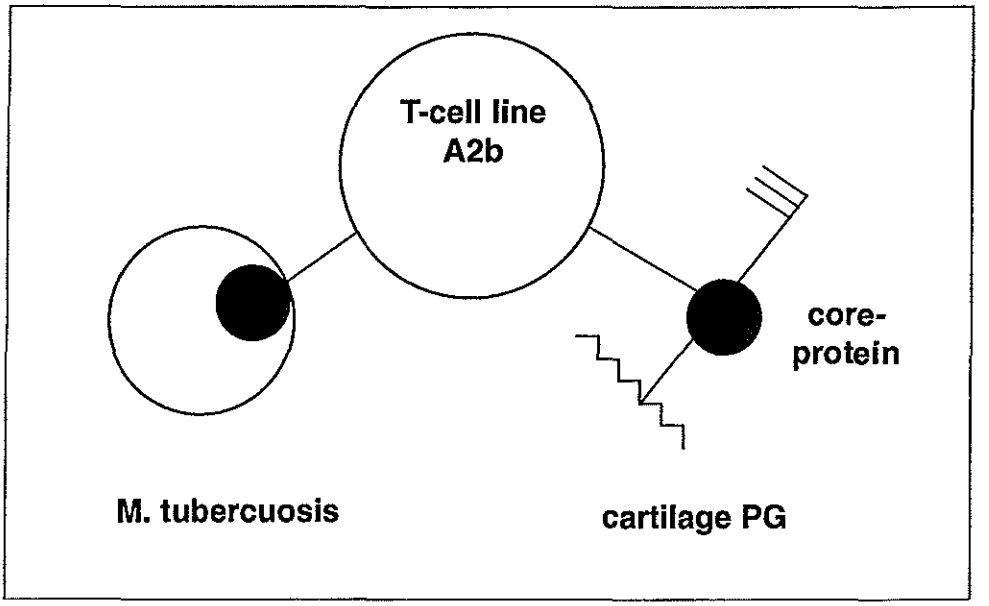

Figure IV.3. Mimicry between M.tuberculosis and cartilage PG.

trauma and spread of M.tuberculosis

Blacklock et al. (8) studied the influence of trauma on the spread of *M. tuberculosis* both in a rabbit and guinea pig model. They injected saline, peptone and penicillin in muscles and joints after inoculation of suspensions of human tubercle bacilli (H.37Rv) into the left ventricle. Histological examination of the site of injection showed in a marked percentage tuberculous lesions. The number of lesions was dependent on the type of injected fluid. Saline showed less reaction in comparison with peptone and penicillin. The not injected side was used as a control and this side did not reveal any alteration. This model was also used to study the influence of a mechanical trauma such as a blow with the edge of a steel chisel under the same conditions. An identical reaction pattern was observed (Figure IV.5.a).
Later Blacklock et al. (8) used a model in rabbits and guinea-pigs, in which they produced a primary lung lesion and studied the haematogenous spread of the bacilli. Insertion of silk threads through muscles at widely separated places one, two, three and four weeks after the inoculation caused the development of secondary tuberculous lesions only around the threads that were inserted in the fourth week after inoculation (Figure IV.5b). They concluded that the time factor was very critical: the spread of the infection by the bloodstream took place shortly *before* the twenty-eight day after inoculation. This phenomenon may explain what happens in man with regard to the occurrence of extrapulmonary tuberculosis, for though all forms of trauma occur frequently, only those that happen in a certain time-period may cause such secondary lesions. As stated by Blacklock the time factor is essential. There must be a bacteriaemia when the local injury takes place; how often this occurs in man is unknown.

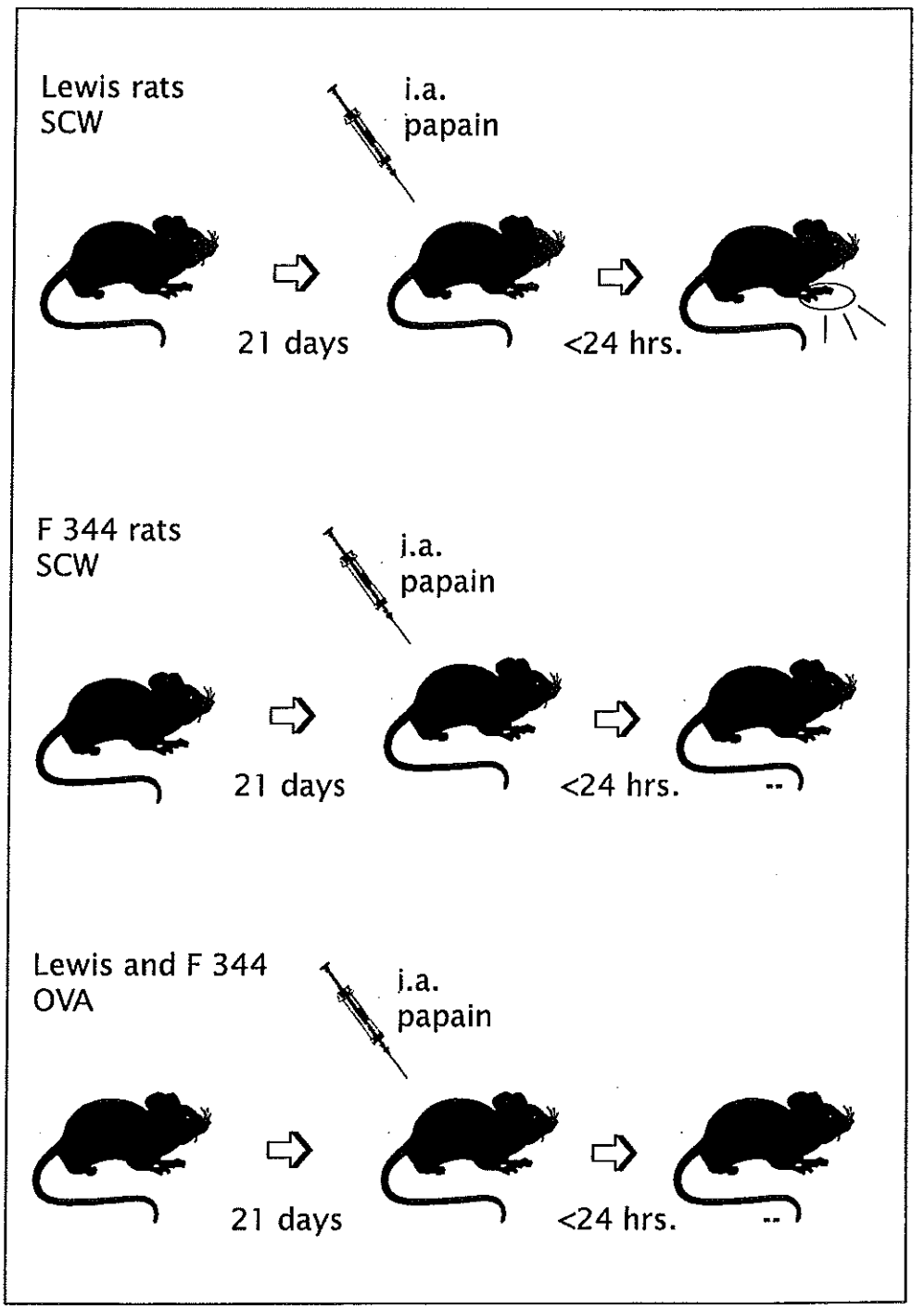

Figure IV.4. SCW model, crossreactiveness and trauma.

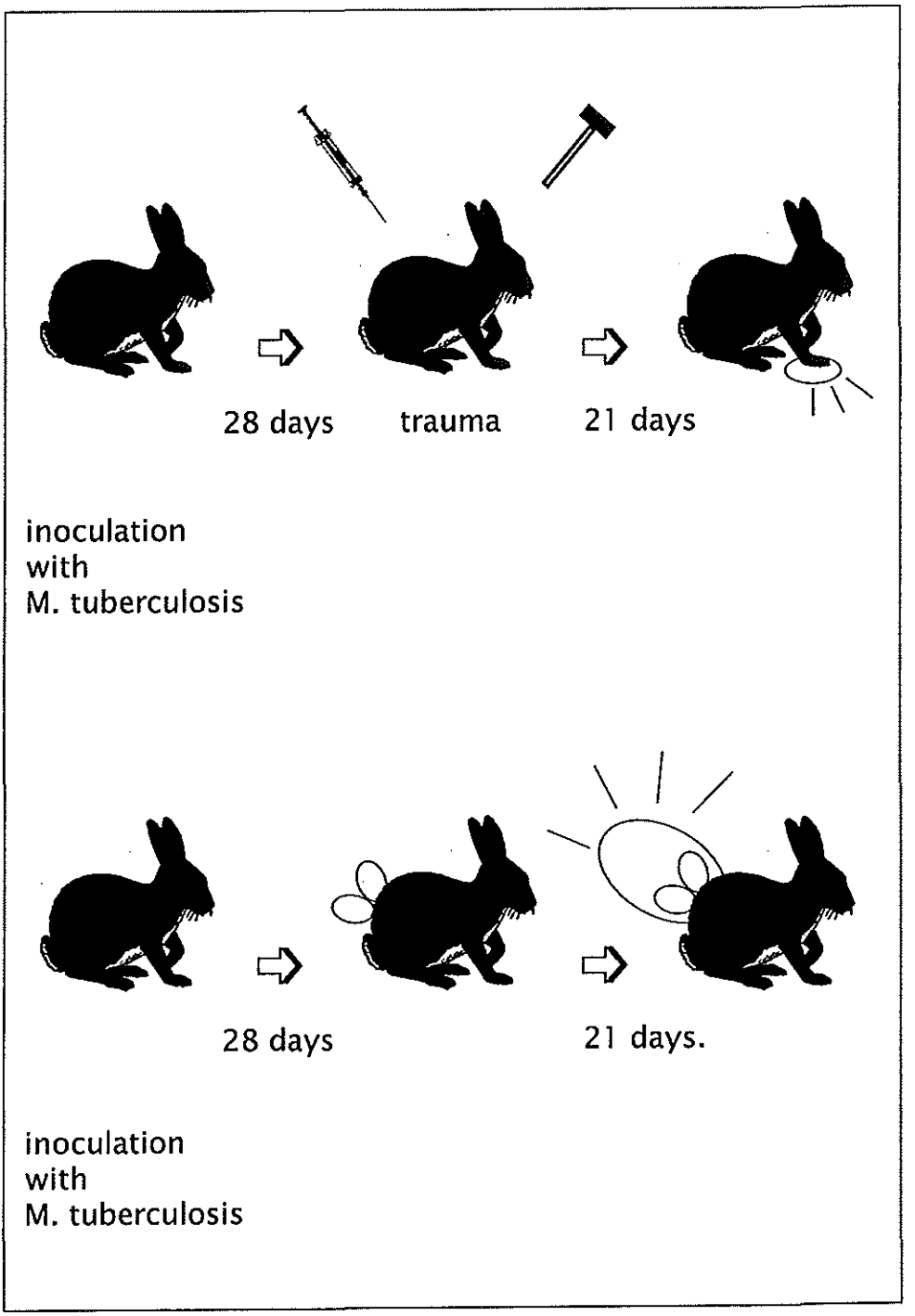

Figure IV.5 Model trauma and spread of M.tuberculosis.

IV.7. Model

All these data should be considered in formulating a theory of the cause of arthritis in general and of the cause of tuberculous arthritis in patients with rheumatoid arthritis in particular. Some host factors determine the type of disease, the details of the clinical response and the time at which an individual is most susceptible. Certain HLA molecules strongly predispose to particular diseases. Certain T-lymphocyte receptor molecules may prove to be more influential and specific in regulating precise clinical and immunological responses. The processing of antigen presenting cells and the subsequent interaction between peptides, HLA molecules and T-lymphocyte receptormolecules are the critical steps in the causation of arthritis. Once this stage has passed the joint is particularly vulnerable because of the possible recognition of shared epitopes. In addition many foreign substances readily enter the systemic circulation and then the joints, particularly after the joints are diseased. Local immunity and antigen recognition by T-cells of *M. tuberculosis* may be diminished at the pulmonary level because the phenomenon of homing is organ specific. Macrophages phagocytise *M. tuberculosis* and have a special attraction to the inflamed joint. At the site of the joint in which there is overactivity, *M. tuberculosis* will be recognised as one of the "common" antigens at which the inflammation is especially directed. A single disease entity is induced by one agent, but probably more often by several different agents. This reflects the vulnerability of the joints of patients with rheumatoid arthritis to infection in general. Persistance of arthritis depends on the continuation of presentation of antigens. Having reached a certain stage the joint is so damaged that this process of antigen presentation is an ongoing process.

Model of extrapulmonary tuberculosis in patients with rheumatoid arthritis.

RA in an immunogenetically susceptible host (45)
elevated levels of antibodies to HSP's (92)

↓

(Re)infection with *M. tuberculosis* in the lung

↓

phagocytosis by macrophages
no/diminished local T-cell reaction because of homing (24,29)
antigen specific T-cells retained in inflamed joint (12,15,64)
predominance of CD4 in synovial membrane (30,70)

↓

haematogenous spread (after 4-6 weeks) (8)
expression of HSP's (arthritogenic factor) (32)
preferential spread to injured joint (8)

↓

preferential presence of bacterium primed mononuclear cells in joint (14)

↓

over-expression of HSP's from local effector mechanism (3,15)
release of lymphokines induces MHC class II expression (5)

↓

recognition of HSP's by T-cells
cross-reactiveness with cartilage components in combination with trauma and/or defective suppression mechanism and/or a failing feedback mechanism (15,41)

↓

cell migration and perpetuation of inflammation (3)

↓

tuberculous arthritis in a RA joint

IV.8. References

1. Aho K, Leirisalo RM, Repo H. Reactive arthritis. Clin Rheum Dis 1985;11:25-40.
2. Allen SC. A case in favour of Poncet's disease. Br Med J 1981;283:952.
3. Allen CA, Highton J, Palmer DG. Increased expression of p150, 95 and CR3 leucocyte adhesion molecules by mononuclear phagocytes in rheumatoid synovial membrane: comparison with osteoarthritis and normal membranes. Arch Rheum 1989;32:947-54.
4. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
5. Backwill FR, Burke F. The cytokine network. Immunol Today 1989;10-299.
6. Beighton P, Solomon L, Valkenburg HA. Rheumatoid arthritis in a rural South African population. Ann Rheum Dis 1975;34:136-41.
7. Bjarnason I, Peters TJ. Helping the mucosa making sense of macromolecules. Gut 1987;28:1057-61.
8. Blacklock JWS, Williams JRB. The localisation of tuberculous infection at the site of injury. J Bact Path 1957;74:119-31.
9. Bradley SF, Vibhagool A, Kunkel SL, et al. Monokine secretion in aging and protein malnutrition. J Leukocyte Biol 1989;45:510-4.
10. Breedveld FC, Trentham DE. Progress in the understanding of inducable models of chronic arthritis. Rheum Dis Clin N Am 1987;13(3):531-44.
11. Breur-Vriesendorp BS, Dekker-Saeys AJ, Ivanyi P. Distribution of HLA B 27 subtypes in patients with ankylosing spondylitis: the disease is associated with a common determinant of the various B27 molecules. Ann Rheum Dis 1987;46:353-6.
12. Broek MF van den, Berg WB van den, Putte LBA van de. Monoclonal anti-1a antibodies suppress the flare up reaction of an antigen induced arthritis in mice with oral antigen. Clin Exp Immunol 1986;66:320-30.
13. Broek MFvan den, Berg WB van den, Putte LBA van de. Streptococcal cell wall induced arthritis and flare up reaction in mice induced by homologous or hetreologous cell walls. Am J Pathol 1988;133(1):139-49.
14. Broek MF van den, Berg WB van den, Artnz OJ. Reaction of bacterium-primed murine T-cells to cartilage components: a clue for the pathogenesis of arthritis ? Clin Exp Immunol 1988;72:9-14.
15. Broek MF van den. T-cell mediated exacerbations of experimental arthritis: a possible mechanism for chronicity. 1988. Thesis University of Nijmegen, The Netherlands .
16. Broek MF van den, Berg Wb van den, Putte LBA van de. The role of mast cells in antigen induced arthritis in mice. J Rheumatol 1988;15:544-51.
17. Broek MF van den, Bruggen MCJ, Putte LBA van de, et al. T-cell responses to streptococcal antigens in rats: relation to susceptability to streptococcal cell wall induced arthritis. Cell Immunol 1988;116(1):216-29.
18. Broek MF van den, Putte LBA van de, Berg WB van den. Crohn's disease associated with arthritis: a possible role for cross reactivity between gut bacteria and cartilage in the pathogenesis of arthritis. Arthr Rheum 1988;31(8):1077-9.

19. Buchanan WW, Murdoch RM. That rheumatoid arthritis will disappear. J Rheumatol 1979;6:324-9.
20. Burmester GR, Dimitru-Bona A, Waters SJ, et al. Identification of three major synovial lining cell populations by monoclonal antibodies directed to Ia antigens and associated with monocytes/macrophages and fibroblasts. Scand J Immunol 1983;17:69-82.
21. Burgos-Vagas, Howard A, Ansell BM. Antibodies to peptidoglycan in juvenile onset ankylosing spondilitis and pauciarticular onset juvenile arthritis associated with chronic iridocyclitis. J Rheumatol. 1986;13:760-7.
22. Calin A, Elswood J, Klouda PT. Destructive arthritis, rheumatoid factor and HLA-Dr4:susceptibility versus severity, a case control study. Arhritis Rheum 1989;32:1221-5.
23. Cavender DE, Haskard DO, Joseph B, et al. Interleukin-1 increases the binding of human B- and T-lymfocytes to endothelial cell monolayers. J Immunol 1986;136:203-7.
24. Cavender D, Haskard DO, Yu CL. Pathways to chronic inflammation in rheumatoid synovitis. Fed Proc 1987;46:113-7.
25. Cavender DE, Edelbaum D, Ziff M. Endothelial cell activation induced by tumour necrosis factor and lymfotoxin. Am J Pathol 1989;134:551-60.
26. Chang YH, Pearson CM, Chedid L, et al. Adjuvant polyarthritis. Induction by N-acetylmuramyl-L-alanyl-D-isoglutamine, the smallest peptide subunit of bacterial peptiglycan. J Exp Med 1981;153:1021-6.
27. Cohen IR. Autoimmunity: physiologic and pernicious. Adv Intern Med 1984;29:147-65.
28. Cohen BJ, Buckley MM, Clewly JP, et al. Human parvovirus infection in early rheumatoid and inflammatory arthritis. Ann Rheum Dis 1986;45:832-8.
29. Dinther-Janssen ACHM van. Adhesion molecules and lymphocyte-cell interactions in the rheumatoid synovial membrane. Thesis 1992 Free University Amsterdam The Netherlands.
30. Duke O, Panayi G, Janossi G, et al. An immunological analysis of lymphocyte subpopulations and their microenvironment in the synovial membranes of patients with rheumatoid arthritis using monoclonal antibodies. Clin Exp Immunol 1982;49:22.
31. Eden W van, Holoshitz J, Nevo Z, et al. Arthritis induced by a T-lymphocyte clone that responds to M.tuberculosis and to cartilage proteoglycans. Proc Natl Acad Sci USA 1985;82:5117.
32. Eden van W, Thole JE, Zee R van der. Cloning of the mycobacterial epitope recognised by T lymfocytes in adjuvant arthritis. Nature 1988;331:171-3.
33. Eden van W, Hogervorst EJ, Hensen EJ, et al. A cartilage mimicking T-cell epitope on a 65K mycobacterial heat shock protein: adjuvant arthritis as a model for human rheumatoid arthritis. Curr Top Microbiol Immunol 1989;145:27-43.
34. Eden van W. Heat-shock proteins and the immune system. Immunol Rev 1991;121:5-28.
35. Epidemiologisch preventief onderzoek Zoetermeer (EPOZ). Vijfde voortgangsverslag deel 4 (reuma) 1979.

36. Fiflit H, Dample SP, Gregory JP, et al. Sera from patients with poststreptococcal glomerulonephritis contain antibodies to glomerular heparansulfate proteoglycan. J Exp Med 1985;161:277-89.
37. Fleming Corbett M, Wood PH. Early rheumatoid disease II Patterns of joint onvolvement. Ann Rheum Dis 1976;35:361-4.
38. Fritzsimons E, Weber M, Lange CF. Monoclonal antibodies to streptococcal cell membrane: in vivo GBM binding with Goodpastures phenomenon. 6th Intern Congr Immunol Abstr 1986;3.48.15.
39. Goroncy-Bermes P, Dale JB, Beachey EH, et al. Monoclonal antibodies to human renal glomeruli cross-reacts with streptococcal M protein. Inf Imm 1987;55:2416-9.
40. Goto M, Miyamato T, Nishioka K, et al. T cytotoxic and helper cells are markedly increased and T suppressor and inducer cells are markedly decreased in rheumatoid synovial fluids Arthritis Rheum 1987;30:737-43.
41. Graeff-Meeder B. Immunereactivity to heat shock proteins in juvenile chronic arthritis. May 1992. Thesis University of Utrecht, The Netherlands.
42. Greenwood BM. Polyarthritis in western Nigeria. Ann. Rheum Dis 1970;29:56.
43. Gregerson PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to the molecular genetics of susceptability to rheumatoid arthritis. Arthritis Rheum 1987;30:1205-13.
44. Guilbert B, Dighiero G, Avrameas S. Naturally occurring antibodies against nine common antigens in human sera. J Immunol 1982;128:2779-87.
45. Harris ED. Rheumatoid Arthritis. Pathophysiology and implications for therapy. Nw Engl J Med 1990;322;18:1277-89.
46. Holoshitz J, Naparstek V, Ben-Nun A, et al. Lines of T- lymphocytes induce or vaccinate against autoimmune arthritis. Science 1983;219:56.
47. Holoshitz J, Matitiau, A Cohen IR. Arthritis induced in rats by cloned T-lymphocytes responsive to mycobacteria but not to collagen type II. J Clin Invest 1984;73:73:211-5.
48. Holoshitz J, Klajman A, Drucker I, et al. T-lymphocytes of rheumatoid arthritis patients show augmented reactivity to a fraction of mycobacteria cross-reactive with cartilage. Lancet 1986;305-9.
49. Holoshitz J, Koning F, Coligan JE, et al. Isolation of CD4-CD8-mycobacteria-reactive T lymfocyte clones from rheumatoid arthritis synovial fluid. Nature 1989;339:226-9.
50. Isaacs AJ, Sturrock RD. Poncet's disease. Fact or fiction? Tubercle 1974;55:135.
51. Jacoby RK, Jayson MI, Cosh JA. Onsert, early stages and prognosis of rheumatoid arthritis: a clinical study of 100 patients with 11 year follow-up. Br Med J 1973;2:96-100.
52. Jalkanen S, Steere Ac, Fox RI, et al. A distinct endothelial cell recognition system that controls lymphocytic traffic into inflamed synovium. Science 1986;233:556-8.
53. Johnson PM, Phua KK, Perkins HR, et al. Antibody to streptococcal cell wall peptidoglycan-polysacharide polymers in seronegative and seropositive rheumatic disease. Clin exp Immunol 1984;55:115-23.

54. Karpus Wj, Swanberg RH. CD4 suppressor cells inhibit the function of effector cells of experimental autoimmune encephalomyelitis through a mechanism involving transforming growth factor-beta 1. J Immunol 1991;146:1163-8.
55. Keat A. Reiter's syndrome and reactive arthritis in perspective. N Engl J Med 1983;309:1606-15.
56. Koch AE, Polverini PJ, Leibovich SJ. Stimulation of neovascularisation by human rheumatoid synovial tissue macrophages. Arthritis Rheum 1986;29:471-9.
57. Koga T, Pearson CM, Narita T, et al. Polyarthritis induced in the rat with cell wall fragments from several bacteria and two Streptomyces species. Proc Soc Exp Biol Med 1973;143:824-7.
58. Koga T, Kotani S, Narita T, et al. Induction of adjuvant arthritis in the rat by various cell walls and their water-soluble compounds. Int Arch Allergy Appl Immun 1976;51:206-13.
59. Kohashi O, Pearson CM, Watanabe Y, et al. Structural requirements for arthritogenicity of peptidoglycans from Staphylococcus aureus and Lactobacillus plantarum and analogous synthetic compounds. J Immunol 1976;116:1635-9.
60. Kohashi O, Kohashi Y, Takahashi T, et al. Suppressive effect of Escherichia coli on adjuvant induced arthritis in germ free rats. Arthr Rheum 1986;29:547-53.
61. Klareslog L. What can we learn about rheumatoid arthritis from animal models? Springer Semin Immunopathol 1989;11:315-33.
62. Krane SM, Goldring MB, Goldring SR. Cytokines in: Cell and molecular bilogy of vertebrate hard tissues. Ciba foundation symposium no 136 New York : John Wiley, 1988;239-56.
63. Lasker HP, Bauer K, Pope RM. Increased helper inducer and decreased suppressor inducer phenotypes in the rheumatoid joint. Arthritis Rheum 1985;31:52-9.
64. Lens JW, Berg WB van de, Putte LBA van de, et al. Flare up of antigen induced arthritis in mice with intravenous antigen: effect of pre-treatment with cobra venom factor and antilymphocyte serum. Clin Exp Immunol 1984;57:520-30.
65. Linos A, Worthington JW, O'Fallon M, et al. The epidemiology of rheumatoid arthritis in Rochester Minnesota: a study of incidence, prevalence and mortality. Am J Epidem 1980;111:87-98.
66. Logtenberg T, Kroon A, Gmelig Meyling FH, et al. Antigen specific activation of autoreactive B cells in in normal human individuals. Eur J Immunol 1986;16:1497-1501.
67. McDermott, McDevitt. The immunogenetics of rheumatoid arthritis. Bull Rheum Dis 1988;38:1-10.
68. Manshady RH, Thompson GR, Weiss JJ. Septic arthritis in a general hospital 1966-77. J. Rheumatol 1980;7:523-30.
69. Meijers KAE, Dijkmans BAC, Hermans J, et al. Non-gonococcal infectious arthritis: a retrospective study. J Infect 1987;14:13-20.
70. Meijer CJ, Lafeber GJ, Cnossen J, et al. T-lymphocyte subpopulations in rheumatoid arthritis. J Rheumatol 1982;9:18-24.
71. Mengle-Gaw L, Conner S, McDevitt HO, et al. Gene conversion between murine class II MHC loci: functional and molecular evidence from the bm12 mutant. J Exp Med 1984;160:1184-94.

72. Mets T, Mubiligi. Rheumatoid arthritis and tuberculosis in Africa. Lancet 1986;1344.
73. Munk ME, Schoel B, Modrow S, et al. T-lymphocytes from healthy individuals with specificity to self-epitopes shared by the mycobacterial and human 65-kilodalton heat shock protein. J Immunol 1989;143:2844-49.
74. Ottenhoff THM, Torres P, Aguas JT de las, et al. Evidence for an HLA-DR4-Associated-immune-response gene for mycobacterium tuberculosis. Lancet 1986;310-2.
75. Pearson CM. Development of arthritis, periarthritis and periostitis in rats given adjuvant. Proc Soc Exp Bio Med 1956;91:95.
76. Philips PE. Evidence implicating infectious agents in rheumatoid arthritis and juvenile rheumatoid arthritis. Clin Exp Rheumatol 1988;6:87-94.
77. Pirzer U, Schonhaar A, Fleischer B, et al. Reactivity of infiltrating T-lymphocytes with microbial antigens in Crohn's disease. Lancet 1991;338:1238-9.
78. Pitzalis C, Kingsley G, Haskard D, et al. The preferential accumulation of helper-inducer T-lymphocytes in inflammatory lesions: evidence for regulation by selective endothelial and homotypic adhesion. Eur J Immunol 1988;18:1997-404.
79. Polla BS. A role for heat shock proteins in inflammation ? Immunol Today 1988;9:134-7.
80. Poncet. De la Polyarthrite Tuberculeuse. Deformante or Pseudorheumatisme chronique tuberculeux. Congres Francaise de chirurgie 1897;1,732.
81. Pope RM, Mc Chesney L, Talal N, et al. Characterisation of the defective autologous mixed lymphocyte respons in rheumatoid arthritis. Arthritis Rheum 1984;27:1234-44.
82. Roudier J, Petersen J, Rhodes GH, et al. The Epstein-Barr virus glycoprotein gp110, a molecular link between HLA DR4, HLA DR1 and rheumatoid arthritis. Scand J Immunol 1988;27:367-71.
83. Roudier J, Petersen J, Rhodes GH, et al. Susceptability to rheumatoid arthritis maps to a T-cell epitope shared the HLA-Dw4DRbeta-1 chain and the Epstein-Barr virus glycoprotein gp 110. Proc Natl Acad Sci USA 1989;86:5104-8.
84. Sanders PA, Grennan DM. Age and year of onset differences in siblings with rheumatoid arthritis. Br J Rheumatol 1990;29:128-30.
85. Severijnen AJ, Kleef R van, Hazenberg MP, et al. Chronic arthritis induced in rats by cell wall fragments of Eubacterium species from the human intestinal flora. Infect Immunol 1990;58:523-8.
86. Severijnen AJ. Human intestinal flora and the induction of chronic arthritis-studies in an animal model. 1990; Thesis Erasmus University Rotterdam, The Netherlands..
87. Silman AJ. Has the incidence of rheumatoid arthritis declined in the United Kingdom ? Br J Rheumatol 1988;37:77-8.
88. Stagg AJ, Harding B, Hughes RA, et al. Peripheral blood and synovial fluid T-cells differ in their respons to alloantigens and recall antigens presented by dendritic cells. Clin Exp Immunol 1991;84:72-7.
89 .L Soloman L, Robin G, Valkenburg HA. Rheumatoid arthritis in an urban South African negro population. Ann Rheum Dis 1975;34:128-35.

90. Spector TD. Rheumatoid arthritis. Rheum Dis Clin North Am 1990;16:513-37.
91. Taguchi O, Nishizuka Y. Self tolerance and localised autoimmunity. Mouse models of autoimmune disease that suggest tissue-specific suppressor T-cells are involved in self tolerance. J Exp Med 1987;165:146-56.
92. Tsoulfa G, Rook, GA Van Embden JD, et al. Raised serum IgG and IgA antibodies to mycobacterial antigens in rheumatoid arthritis of humans. Ann Rheum Dis 1989;48:118-23.
93. Summers GD, Jayson MIV. Does Poncet's disease exist? Rheum. and Rehab. 1980;19:149.
94. Valkenburg HA. Rheumatoid arthritis, pregnancy and the pill-conflicting evidence. In: Rheumatology, current medical literature. Royal Society of medicine, 1986;5:161-3.
95. Venables PJW. Infection and rheumatoid arthritis. Curr Opin Rheumatol 1989;1:15-20.
96. Vollenhoven RF van, Soriano A, McCarthy PE, et al. The role of immunity to cartilage proteoglycans in adjuvant arthritis . Intravenous injection of bovine proteoglycan enhances adjuvant arthritis. J Immunol 1988;331:171-3.
97. Weichman BM. Rat adjuvant arthritis: a model of chronic inflammation. Pharmacol Methods Control Inflamm 1989;5:363-80.
98. White DG, Woolf AD, Mortimer PP, Cohen BJ, et al. Human parvovirus arthropathy. Lancet 1985;1:419-21.
99. Yang XD, Gasser J, Riniker B, et al. Treatment of adjuvant arthritis in rats: vaccination potential of a synthetic nonapeptide from the 65kDa heat-shock protein of mycobacteria. J Autoimmun 1990;3:11-23.
100. Young DB. Stress protein as antigens during infection. In: Rice Evans C Winrow V Blake D Burdon R (eds): "Stress proteins and inflammation". London: Richelieu Press, 1991.
101. Yu CL, Haskard DO, Cavendar D, et al. Human gamma interferon increase the binding of T-lymfocytes to endothelial cells. Clin Exp Immunol 1986;62:554-60.
102. Zee R van der, Eden W van, Meloen RH, et al. Efficient mapping and characterization of a T-cell epitope by the simultaneous synthesis of of multiple peptides. Eur J Immunol 1989;19:43-7.
103. Zhang ZY, Lee CS, Lider O, et al. Suppression of adjuvant a in Lewis rats by oral administration of type II collagen. J Immunol 1990;145:2489-93.
104. Soria LM, Sole JM, Sacanelli AR, et al. Infectious arthritis in patients with rheumatoid arthritis. Ann Rheum Dis 1992;51:402-3.

V. *Radiology of the chest in tuberculosis and rheumatoid arthritis*

V.1. Tuberculosis

infection and disease

In nature, infection without clinical disease is rather the rule than the exception (2,15,19). However, in some infectious diseases infection and disease are synonymous. This is far from the case in tuberculosis. This distinction between infection and disease is not merely semantic and traditional but is in fact quite useful. Most individuals who become infected with *M.tuberculosis* never develop tuberculosis; i.e, the only sign of infection being a positive tuberculin skin test. Obviously however, disease can only develop in those who are infected. If a chest X-ray is made during the 6 to 8 week period after the infection, there may be a small shadow at the site of the infection. There may also be a transient hilar adenopathy (though this is less common in recently infected adults than in children (2)). This small shadow may later calcify or disappear. So after the development of hypersensitivity, healing is the rule, with calcification sometimes subsequently occurring in both the peripheral lesion and the nodes forming the so called Ghon complex (23). The sputum is hardly ever positive on culture at this time. Tuberculosis is considered when the infection has produced clinically detectable pathology. Primary tuberculosis, for instance, is usually only a clinical manifestation of what was described as a transient parenchymal infiltrate and hilar adenopathy.
Primary tuberculosis may become progressive and produce pulmonary symptoms, but more often it is discovered on routine radiological evaluation of asymptomatic tuberculin-positive contacts of an infectious case of tuberculosis. The most common objective finding in post-primary pulmonary tuberculosis is a radiological abnormality of the upper zone of one or both lungs.
If there is an infiltration in the apical or posterior segment of an upper lobe, tuberculosis should be prominently listed among the diagnostic possibilities. Although these are the segments of predilection the possibility of tuberculosis is not excluded when other segments are involved (10).

The only proof of etiology is a positive culture for *M.tuberculosis*. Finding the organisms on a sputum smear gives a presumptive diagnosis and suggests a large population of microorganisms. Symptoms may or may not be present.
Nevertheless, the detection of tuberculosis on the basis of suggestive or classical presentation is less common than detection today because of routine procedures. These include the chest X-ray of older persons admitted to hospital and submission of sputum for smear and culture in older patients with any type of pulmonary symptoms accompanied by cough. A special problem in this respect is that professionals seem to be less vigilant for tuberculosis than they used to be also because they have far less experience than their colleagues had a few decades ago (21,26). Occasionally the finding of anemia of chronic infection initiates further evaluation, eventually resulting in the diagnosis of tuberculosis.

patterns

The chest X-ray is of particular importance. Fraser and Pare (7) list 17 patterns of radiological abnormalities seen in pulmonary disease. Characterisation of the X-ray patterns immediately narrows the diagnostic possibilities to a relatively small number in each pattern. Of the 17 patterns, tuberculosis is considered a possible diagnosis in 12. Even though some of these are unusual patterns for tuberculosis, this disease can produce a wide variety of chest X-ray patterns as shown in the following list in order of descending likelihood:

1. Inhomogenous opacity without recognizable segmental distribution (typical of reactivation tuberculosis).
2. Cystic or cavitary disease.
3. Solitary pulmonary nodule(s) less than 6 cm in diameter.
4. Inhomogenous opacity of recognizable segmental distribution (tuberculous bronchiectasis).
5. Hilar and mediastinal node enlargement.
6. Pleural effusion unassociated with radiological evidence of other disease in the thorax.
7. Diffuse pulmonary disease with a predominantly nodular reticular or reticular nodular pattern (miliary tuberculosis).
8. Homogenous opacity of recognizable segmental distribution (atelectasis-usually in primary tuberculosis).
9. Homogenous opacities without recognizable segmental distribution (acute tuberculous pneumonia).
10. Mediastinal widening.
11. Pleural effusion associated with radiological evidence of other disease in the thorax.
12. Unilateral lobar or segmental pulmonary oligemia (usually from nodal compression).

If any of these radiological patterns is seen, diagnostic considerations should include tuberculosis.

These roentgenographic patterns of pulmonary tuberculosis are often sufficiently characteristic to arouse suspicion of the radiologist and to instigate appropriate investigations to exclude or confirm tuberculosis.

differential diagnosis

Although the radiological appearance is highly suggestive of tuberculosis, the shadows cannot be distinguished with certainty from those of other diseases, including bacterial pneumonias, bronchogenic carcinoma, metastatic carcinoma, lung abscess or mycotic diseases.

Older and more indolent lesions of tuberculosis are more likely to to be recognizable because of associated localised fibrosis, with or without calcification and distortion of the trachea and main bronchi. The presence of cavitation is of prime importance as an indicator of possible active and communicable tuberculosis. However cavities are not specific for pulmonary tuberculosis and appear in many other lung diseases (6).

Comparison of serial X-rays is frequently necessary to evaluate tuberculosis activity. Whenever possible, previous X-rays should be obtained for comparison even if considerable effort is required. Many different problems are solved when X-rays taken a long time earlier are compared with current films and no change is found in shadows that were thought to be acute disease on recent films (28).

reliability

The lack of reliability in the interpretation of X-rays has been repeatedly demonstrated in cases of tuberculosis. Expert radiologists and expert chest physicians have participated in extensive re-test studies that reveal a margin of "error"(inconsistent diagnosis) of about 25% . Similar "observer errors" have been demonstrated in many other clinical situations (25).

The extent of tuberculosis of the chest is determined by plain chest roentgenograms in two projections either or not supplemented by CT-scanning.

calcification

Calcification may be present both in the pleura and/or the parenchyma.

It may follow after a pleurisy, such as an empyema, intrapleural hemorrhage, or previous pneumothorax treatment for tuberculosis. Exposure to asbestos presumably produces pleural calcification by irritation (chemical and/or mechanical) related to the asbestos fibers in the pleura. The common feature of these disorders is a chronic fibrinous pleuritis in which calcium is subsequently deposited (24). The radiological shadow of intrapleural calcification produces a characteristic pattern, but one that can simulate parenchymal disease and cause confusion to those unfamiliar with chest X-rays. Slightly overexposed posterior-anterior and lateral or oblique projections enhance the recognition of calcified pleural plaques (22).

Calcification is most commonly seen in the diaphragmatic pleura, particularly on the lateral projection. It is probable that only calcified regions are seen on chest X-rays because sites that do not contain calcium are too thin to produce detectable differences in radiodensity. If the patient is followed for a period of years, plaques may seem to enlarge and become more numerous; however, at least some of this change represents increasing calcification rather than actual growth of the lesions (9). Bilateral ovoid or lenticular shaped pleural plaques of uniform density are a common radiological manifestation of exposure to asbestos. Inflammatory disease and traumatic injury to the pleura with haematoma formation can produce calcified lesions of similar appearance, but these are almost always unilateral and localized. The presence of typical bilateral pleural plaques is virtually pathognomonic of exposure to asbestos (3).

In tuberculosis, calcification in the parenchyma often occurs in a previously caseous area. The calcific material may be found microscopically in the form of fine dust-like granules, larger particles, or extensive solid masses. The chemical composition of the calcium salt in calcified, caseous material is essentially the same as in normal bone. The predominant salt is calcium phosphate. Why some caseous areas become calcified and others, even in the same person do not, is not clearly understood, mainly because the mechanism of the deposition of calcium phosphate in

necrotic areas in general is not elucidated. Calcification of caseous areas tends to occur more frequently and to a more marked degree in childhood than in adult life. This may be related to the fact that the plasma contains a larger amount of phosphorus in children.

The rate at which calcification occurs in different lesions is, doubtless, dependent upon the calcium-phosphorus content of the plasma and upon the chemical composition of the necrotic area. Deposition can occur in 24 hours (20).

The calcification of a tuberculous caseous area to a degree that will render the calcification visible in chest X-rays requires a much longer period of time. In the case of infants in Lubeck (18) who were given virulent tubercle bacilli by mistake instead of BCG and in whom the time of the infection could therefore be accurately dated, calcification was found at autopsy as early as 58 days after the ingestion of the bacilli. The earliest appearence of calcification in the chest X-rays was at 14 months. Brailey (4) observed the appearance of radiologically visible calcification in a 10 month'old infant who became tuberculine positive when 6 weeks old.

Ossification of calcified primary lesions is a frequent occurrence. True bone develops, often with typical marrow containing the usual bloodforming elements. Ossification of calcified lesions of reinfection may also occur, but, at least in adults, this appears to be decidedly less frequent than the ossification of primary lesions of childhood. Whether primary lesions occurring in adults have the same tendency to ossify as in children is not known, nor is the underlying reason for the ossification of childhood primary lesions clear. It is well known that ossification occasionally occurs in the viscera in calcified lesions of whatever origin. The conditions that determine its occurrence are not understood.

It has been stated by a number of authors that caseous material cannot be absorbed. Marchand (13) writes:"Once caseation has occurred it is obvious that resorption is no longer possible" Aschoff (1) and others have expressed the same opinion. There is however ample evidence that caseous material can be absorbed. This is clear from the studies of Willis (27) and of Oppenheimer (16), whose observations have been confirmed by Burke (5) The precise manner of absorption of caseous material has not yet been determined, but it is clear that in the instances in which liquefaction occurs absorption is easily possible. During the process of absorption some of the unsoftened caseous material may be ingested by macrophages, in the manner in which they ingest other dead cellular material during the process of repair that is familiar at sites at which tissue has been destroyed by any injurous agent. Finally it may be noted that calcium salts, once deposited in a tuberculous lesion, need not remain permanently at the site. Brailey (4) describes the gradual rarefaction and complete disappearence of visible calcification from a lesion in a child examined periodically by means of X-ray.

V.2. Rheumatoid arthritis

The pulmonary manifestations of rheumatoid arthritis may include pleural inflammation with or without effusion, interstitial fibrosis, pulmonary nodules, Caplan's syndrome and pulmonary vasculitis (11). Of these, interstitial fibrosis seems to be the most common although the frequency of occurrence of any of the manifestations is not well established. The reported prevalence of rheumatoid involvement of the lungs and pleura varies considerably (8). This at least in part relates to the means by which patients were evaluated. Approximately one-third of patients with rheumatoid arthritis will have pulmonary involvement as indicated by an abnormal chest X-ray, a reduced diffusing capacity or both, whereas patients with osteoarthritis do not have similar abnormalities. Radiological abnormalities were noted in one half of those with abnormal pulmonary function tests. In patients with extra-articular features of rheumatoid arthritis, pulmonary fibrosis occurs radiologically in approximately 20 percent (17). Although rheumatoid arthritis is more common in women, fibrosis is more common in men. Pulmonary fibrosis has been reported to precede, to occur at the same time as, or to follow the appearence of joint symptoms. In general, it appears that the fibrosis associated with rheumatoid arthritis progresses only slowly or not at all once it is established, although occasionally deaths from respiratory insufficiency have occurred (11).

Pulmonary fibrosis associated with rheumatoid arthritis cannot be distinguished from idiopathic pulmonary fibrosis by clinical, physiological, radiological, or histological criteria. The diagnosis is based on the findings supporting the diagnosis of rheumatoid arthritis.

The frequency of pleural involvement in patients with rheumatoid arthritis is also variable, ranging from 2 to 22 per cent in clinical series and as high as 52 per cent in an autopsy series (12). The effusion tends to follow the appearence of symptoms in the joints, often many years later; however, approximately 50 per cent of effusions occur within 5 years of the appearence of joint symptoms. As with pulmonary fibrosis, effusion occurs more often in men than in women. Rheumatoid pleuritis is usually benign and resolves spontaneously in several weeks to months but usually leaves residual pleural thickening (8,14).

Rheumatoid nodules in the lung usually occur in patients with subcutaneous nodules, although their frequency has not actually been established. The lung nodules may be single or multiple and solid or (occasionally) cavitary. They vary in size from a few millimeters to 7 to 8 cm. Often either pleural or parenchymal disease is also present. Histologically the pulmonary nodules are identical to the subcutaneous nodules. The activity of the nodules tends to parallel that of the systemic process as does their response to treatment. Treatment of the nodule itself is not necessary except in the unusual occurrence of hemoptysis from a cavitary lesion. Caplan's syndrome is an accelerated formation of nodules that occurs in patients who have both rheumatoid arthritis and pneumoconiosis. It was initially described

in coal workers but subsequently has been noted in association with other causes of pneumoconiosis. The histological findings are similar to those of a necrobiotic rheumatoid nodule although recognizable dust particles may also be present (11).

V.3. References

1. Aschoff L. Uber die naturlichen Heilungsvorgange bei der Lungenphthise Verh d Deutsch Kong. f inn Med 1921;33:14.
2. Bailey W C. Diagnosis of tuberculosis. in: Clinics of Chest Medicine 1980; 1;2:209-17 Philadelphia, W B Saunders Co.
3. Becklake MR. Asbestos related diseases of the lungs and other organs: their epidemiology and implications for clinical practice. Am Rev Resp Dis 1976;114:187.
4. Brailey. Observations on the development of intrathoracic calcification in tuberculin-positive infants. Bull Johns Hopkins Hosp 1937;61:258.
5. Burke H E. Tuberculosis in rabbits. Am Rev Tuberc 1940;42:343.
6. Edwards PQ. Screening for tuberculosis. Chest 1975;68 (suppl):451.
7. Fraser RG, Pare JAP eds.: Diagnosis of diseases of the chest. 1979 W B Saunders Co. Philadelphia.
8. Harmon C, Wolfe F, Lillard S, et al. Pulmonary involvement in mixed connective tissue disease. Arthritis Rheum 1976;19:801.
9. Heller RM, Janower ML, Weber AL. The radiological manifestations of malignant pleural mesotheliomas. Am J Roentgenol 1970;108:53.
10. Hinshaw HC, Murray JF, eds.: Diseases of the chest. Philadelphia, W B Saunders Co. 4th ed., 1980 .
11. Hopewell PC. Idiopathic pulmonary fibrosis and collagen vascular diseases. Diseases of the chest. 1980 WB Saunders Philadelphia.
12. Hunninghake GW, Fauci AS. State of the art: Pulmonary involvement in collagen vascular diseases. Am Rev Resp Dis 1979;119:471.
13. Marchand F. Zur pathologischen Anatomie und Nomenklatur der Lungentuberkulose. Munch med Woch 1922;69:55.
14. McAdam LP, O'Hanlan MA, Bluestone R, et al. Relapsing polychondritis: Prospective study of 23 patients and a review of the literature. Medicine 1976;55:193.
15. Middlebrook G. Tuberculosis and science. Am Rev Resp Dis 1982;125(3):5-7.
16. Oppenheimer EH. Experimental studies on the pathogenesis of epituberculosis. Bull Johns Hopkins Hosp 1935;57:247.
17. Popper MS, Bogdonoff ML, Hughes RL. Interstitial rheumatoid lung disease. A reassessment and review of the literature. Chest 1972;62:243.
18. Reichsgesundheitsambt. Die Sauglingstuberkulose in Lubeck. Arbeit a. d. Reichsgesndhtamte 1935,69.
19. Rich AR. The pathogenesis of tuberculosis. 1951 Thomas CC Publ Illinois.
20. Schmidt MB. Die Verkalkung. Hdbch d all Path. Krehl and Marchand Leipzig 1921 BdIII,Abt2,215.
21. Sluiter HJ, Knol K. Tuberculose in Nederland anno 1988. Ned Tijdschr Geneeskd 1989;133,2:59-60.
22. Soutar CA, Simon G, Turner Warwick M. The radiology of asbestos-induced diseases of the longs. Br J Dis Chest 1974;68:235.

23. Stead WW, Kerby GR, Schluter DP, et al. The clinical spectrum of primary tuberculosis in adults. Ann Int Med 1968;68:731.
24. Taryle DA. Lakshminarayan S Sahn S A. Pleural mesotheliomas-an analysis of 18 cases and review of the literature. 1976;55:153.
25. Toman K. Tuberculosis case-finding and chemotherapy. How reliable is chest radiography. WHO Geneva 1979.
26. Veen J, Steensma JT. Tuberculose, nog altijd een uitdaging. Ned Tijdschr Geneeskd 1989;133,2:61-5.
27. Willis HS. The specificity of pulmonary consolidation in tuberculous patients(epituberculosis). Am Jour Roentgenol 1934;31:721.
28. Yerushalmy JM, Garland LH, Harkness JT, et al. Evaluation of the role of serial chest roentgenograms in estimating progress of disease in patients with pulmonary tuberculosis. Am Rev Tuberc 1951;64:225.

VI. *An explosion of predominantly extrapulmonary tuberculosis in a general practitioner's practice.**

Introduction

In august 1988 a general practitioner from the local community of Veghel reported to the Regional Medical Officer of Health (RMOH) for the province North Brabant that since the middle of 1987 he had seen eight patients in his practice in whom tuberculosis was diagnosed. Because of this signal the RMOH started an official investigation.

After retiring from his normal activities as a general practitioner two years before, the doctor had continued a part of his activities. These activities consisted of the treatment of patients with complaints of the joints in general and RA in particular. Besides these diseases he also treated patients with various backproblems, patients with skin ulcers of the leg (ulcus cruris) and patients with unspecified pain problems.The treatment for the patients with RA consisted of a combination of several drugs. In combination with the intravenous administration of vitamin C he applied a spray which contained a 20% solution of Lidocaine intranasally. He also administered phenylbutazone intramuscularly and a corticosteroid (usually triamcinolone) intramuscularly or intra-articularly. The supposed benefits of this therapy are postulated by Lohman (15). The parenteral form of phenylbutazone- which was abandoned as a regular therapeutic on an advice from the Medicines Evaluation Board in the Netherlands (6)- was bought from a pharmacist in Belgium.

Analysis of the data of the eight patients with tuberculosis demonstrated no other common denominator than a visit to the practice in the previous year. The localisation of the tuberculous process was in most cases surprising, namely extrapulmonary. In these eight cases the following localisations were found: soft tissue around the shoulder (1 patient), a carpal joint (2 patients), a knee (1 patient), pulmonary (1 patient), pulmonary and a carpal joint (1 patient) and the soft tissue around the cervical spine.

According to the "stone in the pond principle" (21) in tuberculosis-surveillance it was decided that all the patients who visited the practice in the years 1987 and 1988 should belong to the first ring and therefore should be checked for the presence of active tuberculosis. These patients were advised by the doctor himself to have a check-up for tuberculosis. Cases in relation to the patients who visited the practice in 1987 and 1988, but who themselves had not visited the practice, were considered to belong to the second ring. In September 1988 the first case from the second ring was reported. This case concerned a child with tuberculous meningitis whose grandmother had visited the practice. Because of this the RMOH gave a public warning through the media. The data that were gathered in a national investigation that was started are presented here.

* A Dutch version of this chapter was published in Ned Tijdschr Geneeskd 1992;136:2475-80

VI.2. Patients and methods

The tuberculosis-units of the municipal health services were asked to report cases in relation to this explosion to the RMOH immediately.

Six patients proved to be smear-positive (Ziehl-Neelsen) for mycobacteria in the course of the investigation. On the basis of the history of these six patients and the extent of the pathology on radiological chest examinition the duration of contagiousness of each of them was estimated (16). Visits to the practice on days that one of these six patients also visited the practice in the period that they were contagious were designated as "positive" days. The total number of patients that were treated in the practice was not precisely known, because of some of them no records were kept. The total number of visitors to the practice was estimated at 550. Data could be gathered of 502 patients (9).From each diagnosed and reported case of tuberculosis (n=55) and from a controlgroup of 149 at random chosen persons from the practice in whom no tuberculosis was diagnosed, age, gender, residence, complaints, treatment, diagnosis, data of visits, number of "positive visits" and kind of treatment were registered. The relation of these variables was studied in two by two tables, establishing the odd's-ratio's (OR) and the 95% confidence limits (CI). Threedimensional tables of the relevant riskfactors were studied. The relations that were found were also analysed by logistic regression-analysis. For all positive cultures phage-typing was performed. A number of these cultures was studied with DNA-fingerprinting (12).

VI.3. Results

Analyses were made of the 55 cases of tuberculosis from the first ring. In eleven cases a solitary pulmonary localisation was found. The rest of the cases were extrapulmonary with or without a pulmonary localisation. These extrapulmonary cases were located in soft tissue (17 in buttocks) and in various joints. The number of persons in the controlgroup (these were visitors of the practice in whom no active tuberculosis was found) was 149.

age and gender

Tuberculosis was found in 18 men and 37 women. The average age of the tuberculosis patients was 58 years (range : 20-84) and of the control group 60 years (range 14-86). There was no significant difference in gender between both groups.

interval between symptoms and diagnosis

Figure VI.1 shows the relation between the first symptoms and the moment of diagnosis during four-week periods. On the basis of their history and radiological examination two patients were considered to have been symptomatic and contagious during the whole of 1987. No information was available on their history in 1986. Of the other patients the earliest traceble symptoms date from the 8th four-week period of 1987. Most cases were diagnosed in the 9th four-week period in which the extended origin and contact tracing took place.

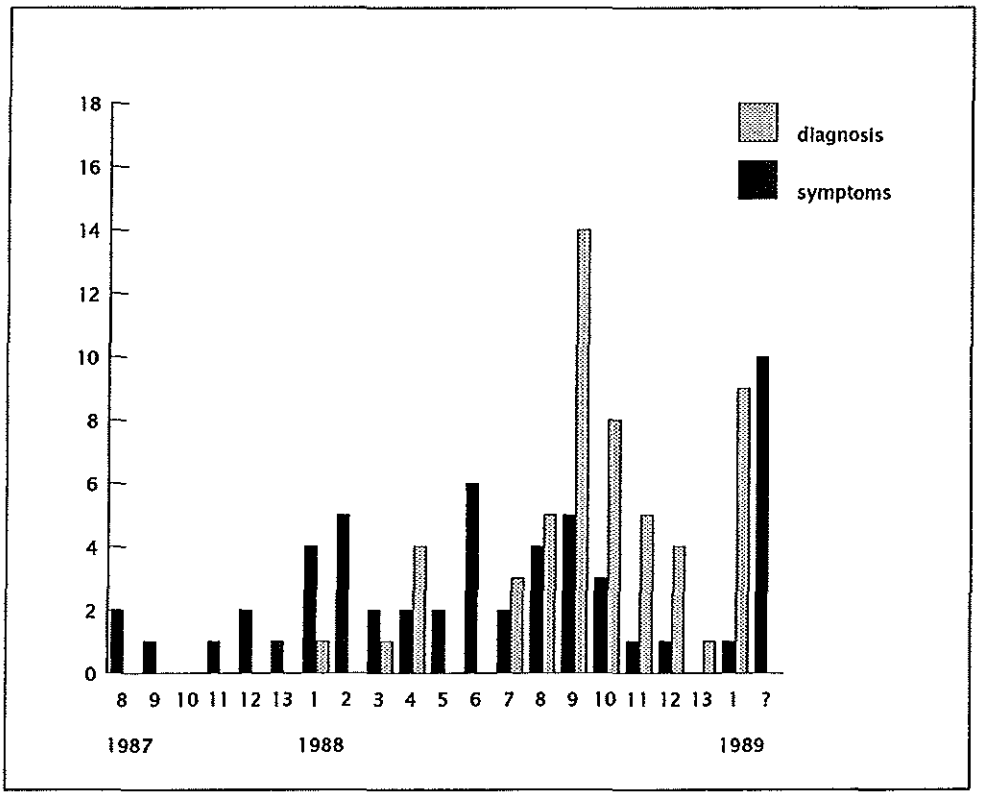

Figure VI.1. Number of new cases of tuberculosis in a general practitioners practice , per four-week periods showing the time of first symptoms and moment of diagnosis.

variables in relation to tuberculosis

No differences were found between the TB group and the controlgroup as far as age, gender and treatment with phenylbutazone were concerned. These variables were not subjected to further analysis.

In table VI.1 the relation between treatment with corticosteroids and active tuberculosis is presented.

the relation between the risk-variables

Table VI.1 shows that the strong relation between the diagnosis "tuberculosis" and the use of corticosteroids was true for patients with RA (OR: 10,2; 95%-CL 1,2-468) as well as for the non-RA patients (OR: 47,6; 95%-CL 7,1-1977). It follows that the relation between tuberculosis and corticosteroids cannot fully be explained by RA alone, because the relation was even stronger in the non-RA group. Among the patients who were treated with corticosteroids, TB was more frequent than among those that were not. (OR: 36,2; 95%-CL: 8,8-313).

table VI. 1. The relation between the risk variables "rheumatoid arthritis" (RA) and "treatment with corticosteroids" and active tuberculosis in patients and a controlgroup in a general practitioner's practice with a tuberculosis explosion.

riskvariable	number of patients		odds ratio *	95%-confidence limits
	tuberculosis (n=55)	no tuberculosis (n=149)		
univariate:				
yes/no RA	29/26	30/119	4,4	2,2-9,1
yes/no treatment with corticosteroids	53/2	63/86	36,2	8,8-313
bivariate:				
RA, yes/no treatment with corticosteroids	28/1	22/8	10,2	1,2-468
no RA, yes/no treatment with corticosteroids	25/1	41/78	47,6	7,1-1977
treatment with corticosteroids yes/no RA	28/25	22/41	2,1	0,9-4,7
no treatment with corticosteroids yes/no RA	1/1	8/78	9,8	0,1-775

*Odds ratio concerning the presence of active tuberculosis in the presence of the riskvariable against the absense of the riskvariable.

In the group of patients with RA the number with active tuberculosis was higher than in those without RA (OR: 4,4, 95% CL 2,2-9,1). It also appeared that there was a clear relation between the number of positive visits and the number of tuberculosis-cases. (χ^2 trend-test: $\chi^2 = 20,4$; $p < 0,001$; table VI.2).

table VI.2. Trend in the relation with the risk-variables "rheumatoid arthritis" and "treatment with corticosteroids" in a general practitioners practice with an explosion of tuberculosis to the number of visits to the gp on days that there was also a visit of a smear positive patients ("positive visit")

variable	***number of "positive" visits***							
	0	**1-5**	**6-10**	**11-15**	**>15**	***n***	χ^2	***p***
TB	1	23	15	9	7	55		
no TB	38	63	36	8	4	149		
total	**39**	**86**	**51**	**17**	**11**	**204**	**20,4**	**<0,001**
RA and TB	1	5	11	5	7	29		
RA, no TB	3	12	11	3	1	30		
total	**4**	**17**	**22**	**8**	**8**	**59**	**8,6**	**=0,003**
corticosteroids and TB	1	21	15	9	7	53		
corticosteroids, no TB	12	24	20	4	3	63		
total	**13**	**45**	**35**	**13**	**10**	**116**	**7,5**	**=0,006**
no corticosteroids, yes TB	0	2	0	0	0	2		
no corticosteroids, no TB	26	29	16	14				
total	**26**	**31**	**16**	**14**	**1**	**90**	**0,4**	**=0,5**

TB is tuberculosis; RA is rheumatoid arthritis

The relation between tuberculosis and corticosteroid-therapy can be explained on the one hand by RA and on the other hand by the larger number of positive visits. Table VI.1 also shows the strong relation between the diagnosis "tuberculosis" and the diagnosis RA in the group of patients that were treated with corticosteroids (OR: 2,1 95%-CL 0,9-4,7). In the group of patients with the same diagnoses this relation was not considered because of the small number (2). The relation between the diagnosis tuberculosis and the number of positive visits was stronger in the group with RA than in the group without RA. (see table VII.2). It seemed that the relation of the same items i.e. tuberculosis/positive visits was also present in the group *without* RA but their number was rather small. A strong relation was found between the diagnosis tuberculosis and the number of positive visits for the group that was treated *with* corticosteroids. This relation could not be demonstrated in the group with the same items but *without* corticosteroids since this only concerned two patients with tuberculosis.

By using logistic regression-analysis which contained these variables so they were corrected for one-another, the relation between the risk-variables corticosteroid-treatment, RA and positive visit frequency with the diagnosis tuberculosis was confirmed.

agent

Eventually it was possible to perform phage-typing of 40 *Mycobacterium tuberculosis* isolates in 39 patients. In phage-typing of M. tuberculosis 5 different types can be distinguished. These can be found by using 9 types of mycobacteriophages. All phagetypes which were found in this explosion belonged to type B. The prevalence in the Netherlands of this isolate is 24 % (10). By using DNA-fingerprinting (RFLP) a striking isomorfism was found (figure VI.2).

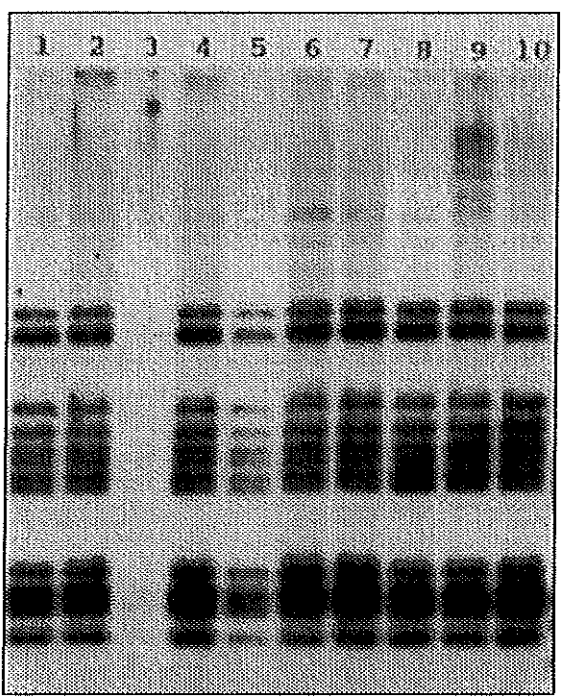

Figure VI.2 *RFLP analysis of isolates of the explosion*

origine and transmission

As source of this exceptional tuberculosis-explosion various possibilities were considered: the doctor himself or one of his assistents, the doctor's dog, one or more patients, and- with regards to the exceptional localisation- the materials that were used for injections. Neither the doctor nor his assistents were found positive for active tuberculosis.

A few weeks before the report to the RMOH the doctor's dog died. A chest X-ray shortly before the his death, showed a intra-thoracic process. Veterinarian expert analysis of this X-ray confirmed a malignancy which excluded this possible source of the explosion. In the course of the investigation it appeared that 6 patients were smear-positive and therefore were contagious. Two of them had visited the practice almost every week for several years. Radiological examination showed extensive pulmonary pathology and it was therefore reasonable to assume that they were contagious during the whole of 1987. It is supposed that one of them was the index-case. The pulmonary localisation in both of these patients was in the upper part of the right lung, which is the preferential site for endogenous reactivation (5,18).

Furthermore it was considered that one of the patients had an unrecognised tuberculous arthritis and that, in combination with an non-sterile injection-technique, this could have caused the explosion. A few weeks before the report to the RMOH the doctor changed his injection technique. Instead of multidose vials he began to use monodose vials. However he always used disposable syringes and needles. Before injection the skin was wiped off with a piece of wedling soaked in ether-petrol. Conclusive proof of this mode of transmission could not be provided.

VI.4. Discussion

Patients in this practice who were treated with corticosteroids and patients with RA were at greater risk of tuberculosis. Patients with RA were frequently treated with corticosteroids. The relation between tuberculosis and corticosteroids could not exclusively be explained by the presence of RA, since this relation also existed in the RA-negative group.
Patients with RA visited the practice more frequently than patients with other complaints. Because of this they had an enhanced chance of being exposed to a patient with a contagious form of tuberculosis. This relation also cannot exclusively be attributed to the presence of RA.

It was not possible to investigate the relation between tuberculosis and a "positive" visit by comparing the data of "yes positive visit" versus "no positive visit" since there was only one patient with tuberculosis who had had no positive visit at all.
Summarising: There are two potential risk factors that were independantly related to the presence of active tuberculosis. These riskfactors were: treatment with corticosteroids and a visit to the practice on a day that there was also a patient with a contagious form of pulmonary tuberculosis. Furthermore a relation between the presence of tuberculosis and RA was found.

Concerning the source of this explosion the following remarks can be made. On the one hand it is possible that there was an exogenous (re)infection with a haematogenous spread to a so called locus minoris resistentiae. On the other hand it is possible that an endogenous reactivation took place. As mentioned before exogenous (re)infection might have been possible due to an inadequate injection-technique. No conclusive proof of this origin can be given. Cultures of nose-aerosol fluids and not used vials of corticosteroids were negative.

exogenous (re)infection

In the group of patients with tuberculosis 38 of the 55 had a tuberculous abscess at the site of the injection. In 47 of the controlpatients there were various infections but not caused by M.tuberculosis, some of them also at the injectionsite. Because of these data it might be assumed that transmission of mycobacteria was by means of injection. The bacteria could be introduced due to defective a-and antiseptic measures.

It is evident that this mode of transmission cannot be proved retrospectively. Another possibility is an exogenous respiratory infection with a haematogenous spread to a locus minoris resistentiae. A recent pulmonary infection might spread via alveolar macrophages that are killed elsewhere in the body. This mode of transmission should be quite unusual in the Netherlands because of the very low infection incidence. Nevertheless there are some arguments in favour of this mode of transmission in this explosion (5,17). In the group of patients visiting the practice the chance of exposure to infection was exceptionally high as compared with the general population. For most patients the time interval between their last actual active contact with *Mycobacterium tuberculosis* must at least be several decades. Immunity and memory may have diminished. It should also be taken into account that treatment with corticosteroids also diminishes the immunological resistance. A joint which is traumatised by an injection during an actual pulmonary infection is predisposed to infection as several experiments and observations have shown (1,13). RA itself also predisposes to a septic arthritis (2). This sort of pathogenesis fits very well with some unsolved historical explosions (11,20) and with some case-reports (4,7,8,14) of extrapulmonary tuberculosis in the literature in which the same kind of pathogenesis was suggested . The relative under-representation of patients with only pulmonary symptoms in comparison with those with extrapulmonary symptoms does not have to be significant in this respect. It might be explained by a difference in local immunity between the pulmonary site and the peripheral site.

endogenous reactivation

Because of their age and the well documented incidence and prevalence rates of tuberculosis in the Netherlands, most patients that visited the practice must have had a primary infection in the past. The average dose of corticosteroids that was administered parenterally in the practice was 12,5 mg a week. In this respect it is reasonable to assume that a carry-over effect has to be taken into account. This is well documented in a study by Cats et al. Six weeks after intra-articular administra-

tion of 25 mg triamcinolonhexacetonide some local effects were still measurable (3). Besides that, some of the patients used other therapeutics that also have the capacity to diminish the immunological reaction: for instance cytostatics in combination with the corticosteroids . In such instances "dormant bacilli" can become active again (19). However, the results of the phagetyping and especially those of the DNA-fingerprinting make this scenario highly improbable: all isolates had the same DNA-restriction pattern. This had not been found before in a random sample of 200 *M.tuberculosis* isolates. However, in all probability this mechanism could have played a role in the index-case. It is known that patients with this kind of endogenous reactivation are more contagious (17).

VI.5. Conclusion

In this explosion of tuberculosis the influence of administration of corticosteroids and a visit on a day that a contagious patient also visited the practice were the most convincing risk factors for acquiring a tuberculosis-(re)infection. Looking at these riskfactors in combination with the data from the bacterial cultures and RFLP-patterns, one can conclude that the most probable mode of transmission must have been either by means of an exogenous aerosol from another patient or by means of injections. There is no convincing evidence for other modes of transmission. It is not possible to find more evidence for the "injection mode". On the other hand experimental data and some well documented cases are consistent with the exogenous aerosol explanation.

VII.6. References

1 Williams JRB. The localisation of tuberculous infection at the site of injury. J Pathol Bact 1957;74:119-31.
2. Brewerton DA. Causes of arthritis. Lancet 1988;ii:1063-5.
3. Cats A, Ijzerloo AG, van Davinova Y, et al. The efficacy of intra-articularly administered MYC 20g5, triamcinolone hexacetonide and placebo in gonarthritis. Scand J Rheumatol 1979;8:199-203.
4. Coope PJ. Tuberculous abscess formation following penicillin therapy. Proc R Soc Med 1947;40:161-2.
5. Douma J. Tuberculose als ziekteproces bij de mens. V 42 VII 23. Leerboek der tuberculosebestrijding. 's-Gravenhage: Koninklijke Nederlandse Centrale Vereniging tot bestrijding van tuberculose, 1984.
6. Drost RA. Toepassing van fenylbutazon en oxefenbutazon beperkt. Ned Tijdschr Geneekd 1984; 128:2367-8.
7. Ebrill Elek SD. Tuberculous abscess formation following intramuscular penicillin. Lancet 1946;ii:379-80.
8. Forbes GB, Srange FG. Tuberculous abscess at the site of penicillin injection. Lancet 1949;i:478-9.
9. Geneeskundige Hoofdinspectie. Staatstoezicht op de Volksgezondheid. Rapport aan de Geneeskundig Inspecteur van de Volksgezondheid voor Noord-Brabant inzake de explosie van voornamelijk extrapulmonale tuberculose. Rijswijk: Geneeskundige Hoofdinspectie, 1990.
10. Groothuis DG. Surveillance by means of phagetyping and surfacespotting. Specific research activities. Geneva: WHO, 1986: T9/181/11.
11. Heycock JB, Noble TC. Four cases of syringe transmitted tuberculosis. Tubercle 1961;42:25-7.
12. Hermans PWM, Soolingen D, van Dale JW, et al. Insertion element IS 986 from M. tuberculosis: a useful tool for diagnosis and epidemiology of tuberculosis. J Clin Microbiol 1990; 28:2051-8.
13. Hortas C, Ferreiro JL, Galdo B, et al. Tuberculous arthritis of peripheral joints in patients with previous inflammatory rheumatic disease. Br J Rheumatol 1988;27:65-7.
14. Hounslow AG. Tuberculous abscess at the site of injection. Lancet 1949;i:709.
15. Lohman AJM. Ervaring met de neusspray. Ned Tijdschr Geneeskd 1952;96:421-4.
16. Meijer J. Enkele opmerkingen over de epidemiologie van de tuberculose. VII 21 Leerboek der tuberculosebestrijding. s'-Gravenhage: Koninklijke Nederlandse Vereniging tot bestrijding der tuberculose, 1984.
17. Nardell E, McInness B, Thomas B, et al. Exogenous reinfection with tuberculosis in a shelter for the homeless. N Engl J Med 1986;315:1570-5.
18. Rijssel ThG van. Pathologie van tuberculose. IV 25. Leerboek der tuberculose-bestrijding. 's-Gravenhage: Koninklijke Nederlandse Centrale Vereniging tot bestrijding der tuberculose, 1984.
19. Steensma J. Tuberculose, gaat het altijd wel goed? Ned Tijdschr Geneeskd 1986;130:145-7.
20. Tamamura M, Ogawa I, Amano S. Observations on an epidemic of cutaneous and lymphatic tuberculosis which followed the use of anti-typhoid vaccine. Am Rev Tub Pulm Dis 1955;71:465-72.
21. Veen J. Tubercle and Lungdisease 1992;73:73-6.

VII. A radiological cohort follow-up study

VII.1. Introduction

In the Netherlands, the age at which a- very rare- first tuberculous infection occurs is shifting more and more to older age groups. This has consequences for the radiological findings. In children an enlargement of the hilar lymph nodes is a rule while in adults this is less frequent (2).
In adults it is quite normal that after a conversion of the Mantoux reaction to positive, a focus in the lung can be found without a hilar reaction. It is also well known that a primary focus is more often not visible on a chest X-ray because the lesion is too small to be detected.

As was concluded in Chapter VI experimental data and some well documented cases are consistent with a thesis of an exogenous aerosol (1,4,5,7,8,10). In fact this would mean that the principal cause of the explosion was a recent case of infectious pulmonary tuberculosis in the waiting room of the doctor's practice, transmitted from one patient to another.
From the available data it is clear that this mode of transmission has played a role since 11 patients of the total of 55 only had pulmonary infection without an extrapulmonary localisation (6). In combination with the other cases of extrapulmonary tuberculosis without a pulmonary localisation this would indeed mean that two transmission modes might have played a role in this explosion.

Nevertheless there remains doubt on the precise source of the explosion and it would mean a coincidence of probabilities.
This consideration raises the question whether it would be possible to exclude definitively a recent pulmonary infection in the exclusively extrapulmonary cases of tuberculosis.

It is hypothesized that patients treated exclusively for extrapulmonary tuberculosis in whom changes on the chest X-ray could be demonstrated several years *after* the explosion which were not yet visible at the first examination in 1988, probably had a recent infection, the time between infection and the first examination being too short to produce detectable lesions.
Confirmation of this in combination with the above mentioned experimental data and the well documented cases would give more insight into the definite source of the explosion in particular and on the pathogenesis of extrapulmonary tuberculosis in general.

VII.2. Patients and methods

The tuberculosis-units of the municipal health services were invited to re-examine by means of a chest X-ray all the patients from the explosion. Together with the X-rays which were made during the first examination in 1987/1988 these roentgenograms were (re)examined by two independent experienced observers. A standardised form was used which contained all the relevant data. The observers had no knowledge of each-other's findings and they were also blinded in relation to the clinical data of the patients.
The most important criterium was the presence of any change between the two roentgenograms and whether this change was thought to be tuberculosis-related. All the patients gave informed consent.

If necessary a control group of 400 roentgenograms could be formed out of the records of the population based tuberculosis control program that were still present in the tuberculosis unit of the municipal health service of Tilburg. This population program was performed in the Netherlands on a legal basis until 1982. In this program each inhabitant of 50 years and older received an invitation for a chest X-ray every two years. The control group would consist of the investigations performed in the years 1970-1975 and would be matched for age and gender. The single criterium for the controls was the presence of a set of two roentgenograms with an interval of at least 4 years.
This controlgroup was thought to give the best comparison because other groups from different available records would give more selectionbias.

VII.3. Results

response

Of the original 55 patients the data suitable for analysis of 30 patients became available.
The non-response of 25 patients was caused by the following factors. Six patients had died in between. Ten patients refused further examination and 9 patients could not be re-examined because the tuberculosis-clinic had no opportunity to cooperate in the study because of lack of personnel and no other services were available.

age

The group responders consisted of 18 female and 12 men. The mean age was 54,6 year (range 22-76).

Of these responders 30 pairs of roentgenograms became available. Of these 30 pairs 7 were from patients that were originally already diagnosed as having pulmonary tuberculosis.

interval

The mean interval in months between the first and the second roentgenogram was 46,5 months and varying from 27 to 70 months (Figure VII.1).

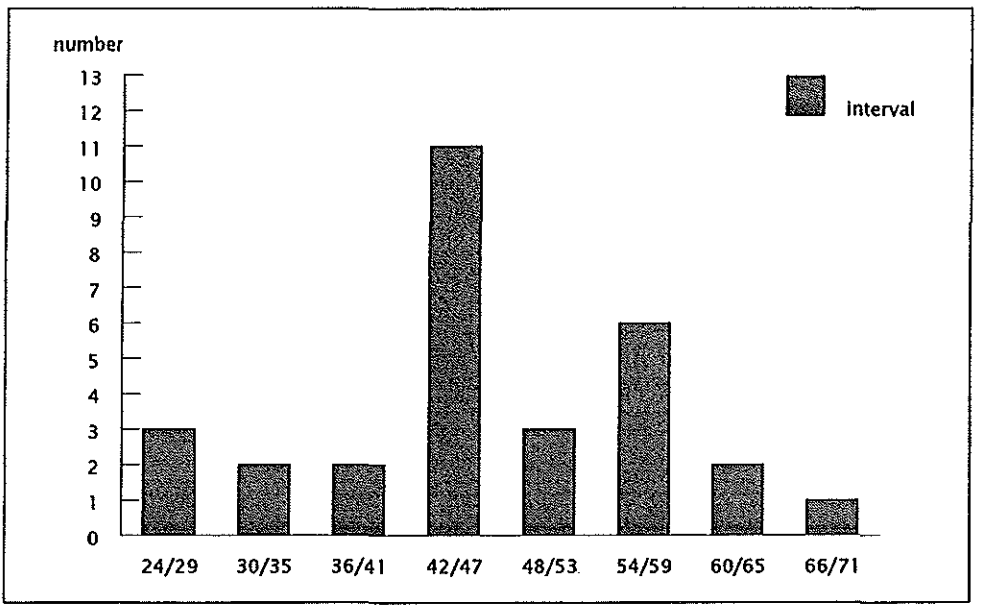

Figure VII.1 Time interval (in months) between first and second roentgenogram.

changes

The investigation showed the following results from the comparison of the old and the new chest roentgenogram:

Table VII.1 The presence of new tuberculosis findings (+) in a comparison of a recent chest roentgenogram in relation to the one at the time of the original diagnosis in patients from the "Veghel explosion".

X-ray findings	-	+	**total**
extrapulmonary tb	21	2	23
pulmonary tb	7	-	7
total			**30**

After re-examination in 1993 two cases had radiological findings on their chest X-ray suggestive of tuberculosis, which findings were not present in 1988 during the national survey in this explosion. Their history will be discussed in more detail.

VII.4. History of two cases

The first case concerns a male born in 1939. He was known with seropositive reumatoid arthritis since 1972. He had no known tb history. He visited the practice in Veghel every two weeks for several years. In 1988 he was present at least 12 times on days that one of the contagious patients also visited the practice. The last "positive" visit was on August 18th. During the national investigation on 29 September 1988 his Mantoux reaction was negative (0 mm). In January 1989 he had a small induration on his left buttock. The Mantoux reaction on the 4th January 1989 was 13 mm. In September 1989 he had abcesses on both buttocks which were incised and the diagnosis tuberculosis was made by culture. He received antituberculous drugs from August 1989 until June 1990 which consisted of 300 mg INH and 600 mg Rifampicin. He probably got pyrazinamide during at least 2 months, but the history of this therapy is uncertain. The chest X-ray of January 1993 was different from those made in September 1988 and January 1989. The difference consisted of a pleural shadow in the inferior region of the right lung. Both investigators suggested this difference was possibly related to tuberculosis.
In February 1989 he suffered a myocardial infarction. In October 1991 he was hospitalised for a pericarditis and a pleuritis. Cultures of inflammation fluids were negative for *M. tuberculosis*. The findings were thought to be either of rheumatoid or tuberculous origin. On clinical grounds it was decided to treat them as being of tuberculous origin.

The second case concerns a female, born in 1923 who visited the Veghel practice for more than ten years with a frequency of about twice a month. In this case further examination revealed that a mistake had been made . The X-ray of 1988 examined by the observers was not of the female but of her spouse who coincidently had a quite similar physiognomy. Re-examination of the original X-rays and comparison with the recent roentgenograms showed indeed no change.

VII.5. Discussion

In general the response in the study was high. On the one hand this might be due to the impact and consequences that the explosion had on the patients, and on the other hand due to the cooperation of the well-organised tuberculosis-surveilance units and and their coordinating organisation the KNCV.
There is no significant difference as far as age and gender is concerned as compared to the original group of 55 patients. The non-response seems not to have any significant influence on the presented results. The cause of death of the 6 patients was in 4 cases directly related to tuberculosis. Five of them had exclusively a pulmonary localisation of the tuberculous process and 1 an extrapulmonary localisation.

The other 2 cases died of a lung carcinoma and a myocardial infarction respectively. Because of the localisation of the tuberculous process the course of the disease in 5 of these cases seems not to be related to the hypothesis of this study.
The interval between the two roentgenograms is almost four years. This seems long enough for the supposed changes.

two cases

In the first case there is a documented change in the Mantoux reaction, suggesting that a primary infection has taken place shortly before (or after) September 1988. One can question whether the extrapulmonary or the pulmonary infection was primary. If the infection was primarily extrapulmonary the infection could probable have taken place in August or perhaps in July by means of an defective injection technique. However, considering the fact that the doctor previous to that time had changed his technique of injection and that he was using disposable material makes this way of transmission less likely; but it cannot be excluded. If the infection took place earlier one might have expected a positive Mantoux reaction but steroids might have influenced this reaction (12).
The pulmonary lesion might have been undetectable in January 1989 because it was still too small or because it was a self-limiting disease because of a good immunological local reaction, which was lacking in the buttocks due to the many previous injections on that location with subsequent tissue destruction (3). The clinical course in 1991 could be due to a pre-existing tuberculous process in the pericardial region. Nevertheless in this case it cannot be concluded that it by any means confirms the hypothesis.

In the second case it was concluded that this was not consistent with the hypothesis.

Since there remained no positive findings that were convincing for changes that were related to tuberculosis there was no need to constitute a control group. From historical data the expected rate of changes in the control group would be 0.0025% (9).

no proof

Since there are no positive findings in favour of the hypothesis this could be explained by the following items.

- The frequency of the supposed changes in the roentgenograms is too small in relation to the number of patients in the study.
- The time needed for the changes in the roentgenograms is longer than four years.

Of these items the first might be possible. It was anticipated that in about 10 percent of the cases the suggested changes really become visible (2).
The second is not appropriate. It is known from data of mass radiography with an interval of three years that three quarters of the newly found smear-positive cases had a normal chest X-ray during a preceding survey (11). Taking the hypothesis into account one could only expect these figures in the study group to be higher in

comparison with the general population. So, on the one hand one can conclude that the hypothesis is not true, but due to the small number of cases this cannot definitely be concluded. This still leaves questions as far as the pathogenesis of extrapulmonary tuberculosis is concerned.

VII.6. Conclusion

In this cohort follow-up study there were no findings that could be interpreted as a proof for the hypothesis that in cases that were primarily and eventually exclusively diagnosed and treated as extrapulmonary tuberculosis it would be possible to demonstrate changes on the chest X-ray several years *after* the explosion.
In this study the finding of an extrapulmonary process in combination with a normal chest X-ray at the moment of the diagnosis of the extrapulmonary tuberculosis suggested that there is no change of the X-ray several years after the diagnosis.

VII.7. References

1. Coope PJ. Tuberculous abscess formation following penicillin therapy. Proc R Soc Med 1947;40:161-2.
2. Douma J. Tuberculose als ziekteproces bij de mens V.22 Leerboek der tuberculosebestrijding. 's-Gravenhage: Koninklijke Nederlandse Centrale Vereniging tot bestrijding van tuberculose, 1984.
3. Drost RA. Toepassing van fenylbutazon en oxefenbutazon beperkt. Ned Tijdschr Geneekd 1984; 128:2367-8.
4. Ebrill Elek SD. Tuberculous abscess kormation following intramuscular penicillin. Lancet 1946;ii:379-80.
5. Forbes GB, Srange FG. Tuberculous abscess at the site of penicillin injection. Lancet 1949;i:478-9.
6. Geneeskundige Hoofdinspectie. Staatstoezicht op de Volksgezondheid. Rapport aan de Geneeskundig Inspecteur van de Volksgezondheid voor Noord-Brabant inzake de explosie van voornamelijk extrapulmonale tuberculose. Rijswijk: Geneeskundige Hoofdinspectie, 1990.
7. Heycock JB, Noble TC. Four cases of syringe transmitted tuberculosis. Tubercle 1961;42:25-7.
8. Hounslow AG. Tuberculous abscess at the site of injection. Lancet 1949;i:709.
9. Styblo K, Geuns HA, van Meijer J. The yield of active case-finding in risk groups. KNCV 1984 vol.22 Selected Papers.
10. Tamamura M, Ogawa I, Amano S. Observations on an epidemic of cutaneous and lymphatic tuberculosis which followed the use of anti-typhoid vaccine. Am Rev Tub Pulm Dis 1955;71:465-72.
11. Toman K. Mass radiography in tuberculosis control. WHO Chronicle, 1976;30:51-57.
12. Veen J. Aspects of temporary specific anergy to tuberculin in Vietnamees refugees. Thesis 1992. University of Groningen. The Netherlands.

VIII. Some clinical data of patients with extrapulmonary tuberculosis.

VIII.1. Introduction

In this thesis the epidemiological analysis of an extraordinary explosion of predominantly extrapulmonary tuberculosis is described. In the follow-up of the cohort many data became available. This chapter contains some of the most relevant data and they will be presented and compared with the data from the literature.

VIII.2. Materials and methods

As described in Chapter VI in 1988 the tuberculosis-units of the municipal health services were asked to examine the patients who were known to visit a doctor in Veghel.
Together with the radiological follow-up as described in Chapter VII an evaluation form was sent to the clinics with questions concerning specific missing data of the patients in relation to the tuberculosis.
The total cohort studied consisted of the 55 patients described in Chapter VI. The patients gave informed consent.

VIII.3. Results

The group as a whole consisted of 18 men and 37 women. Of the 55 patients 3 had a previously recorded history of tuberculosis.
Since not all clinics participated in this second survey and not all records of the patients were complete the total score may differ for different items.

diagnosis

The diagnosis for which treatment was started at the practice is listed in Table VIII.1

Table VIII.1 Diagnosis for which treatment was started in the practice.

	male	female	total
RA	10	19	29
Arthrosis	4	10	14
PHS	-	3	3
Epicondylitis	1	1	2
HNP/ischialgia	3	1	4
Leg ulcer	-	1	1
Fibromyalgia	-	2	2
Total	**18**	**37**	**55**

The mean age at which the rheumatoid arthritis caused the first complaints was 41 years. (range 20-62) and the mean age at which the athrosis became symptomatic was 58 years (range 51-71). The average duration of the RA process before the explosion in the practice was 11 years in patients with RA (range 2-37) and of the arthrotic process 7 years (range 1-18) in patients with arthrosis.
The frequency of general symptomatology in patients with extrapulmonary and pulmonary tuberculosis was recorded.

Table VIII.3. General symptomatology in patients with pulmonary (n=11) and extrapulmonary tuberculosis (n=44).

	extrapulm. tb	pulmon. tb
fever	8	4
nightsweat	5	5
weightloss	8	8
cough	-	8
malaise	14	4
not known	6	3

local symptomatology

All the extrapulmonary cases showed signs of pain, swelling and abscess formation. In at least twenty of the extrapulmonary cases one or more fistula were reported. In five cases these fistula developed after a diagnostic puncture in all but one without the slightest suspicion of a tuberculous process. The shortest reported duration of a fistula was six weeks and the longest 18 months. The average duration of a fistula was five months.

localisation

The division of the extrapulmonary processes was as follows.

Table VIII.4. Localisation of the extrapulmonary processes.

Meningeal membranes	3
Shoulder	6
Upper arm	2
Elbow	2
Wrist	2
Hand	3
Spine	2
Buttock	17
Hip	3
Knee	13
Foot	1
Urogenital tract	2

Fourteen patients had more than one localisation of a tuberculous process. In three of these fourteen cases miliary tuberculosis was diagnosed with the specific radiodiagnostic pattern on the chest X-ray. The following combinations were found:

- Metatarsal/Urogenital tract/knee/lungs
- Buttock/upperarm/thumb
- Shoulder/metatarsal/buttock/pleural membrane
- Meningeal membranes/wrist
- Hip/knee
- Urogenital tract/lungs
- Arm/meningeal membranes
- Knee/knee
- Buttock/buttock
- Buttock/lungs (3x)
- Knee/lungs (2x)

the tuberculin skin test response

During the national survey the response to the tuberculin skin test was performed in 24 patients. The average diameter of the reaction was 17.6 with a range from 2-35. In all other cases the skin test was not performed or data were not suited for analysis ("positive/negative").

diagnosis

In table VIII.1 the results of diagnostic procedures as they were mentioned in the report of the Chief Medical Officer and the patient records are summerized.

Table VIII.1 Outcome of diagnostic procedures in 55 patients with extrapulmonary or pulmonary tuberculosis or a combination of both.

	extrapulm. tb	**pulm. tb**
ZN + cult.+ biopsy +	5	2
ZN - cult.+ biopsy +	0	0
ZN - cult.- biopsy +	1	0
ZN + cult.+ biopsy -	3	3
ZN - cult.+ biopsy -	2	0
ZN - cult.+	5*	1
ZN + cult -	3	0
ZN +	3	0
Cult. +	7	2
Biopsy +	3	0
ZN + cult.+	14	3
Cult.+ biopsy +	1	0
ZN - cult.- biopsy-**	1	0
not known	1	0
Total	**48**	**11**

* 1 positive culture from urinary tract

** Had antituberculous treatment in previous two months.

Therapy

medicamentous

All patients received antituberculous therapy in the combination INH/pyrazinamide and rifampicine. In 16 cases also ethambutol was administered and in 11 cases also streptomycine. The indication for these additional drugs and the duration of this therapy are not clear.

surgical

Of the 55 patients at least 27 underwent one or more operations. In 8 cases it is certain that no operations were performed and in the remaining cases data could not be evaluated. In 18 patients an incision of an abcess and subsequent drainage was performed. In 5 cases this procedure had to be repeated at least once. Other operations that were reported are: amputation digit III (1x), removal of prosthesis

of the hip because of tuberculosis (3x), lymph node excision and skin-grafting (1x), synovectomy (2x), arthrodesis (1x).

Side-effects of medicamentous therapy
In 18 of the 55 patients side-effects from antituberculous therapy were reported. In 9 cases the pyrazinamide therapy caused hepatotoxic symptoms. In three of these cases the therapy had to be stopped and in the other cases the dosage was adjusted. Rifampicine caused stomach complaints in 5 patients. In one case this therapy had to be stopped because of these complaints. Four other cases had a temporary skin rash, probably due to isoniazide.

hospitalisation

Data of the number of hospitalisations because of tuberculosis and the duration of these hospitalisations became available for 37 patients. The total number of hospitalisations of these patients was 54 (range 1-5) and the average stay in hospital per patient was 2,2 months (range 2 weeks-16 months). The average stay in a nursing home is not included in this figure.

final results

Between the onset of the explosion and this study 6 patients had died. Four of them had a cause of death directly related to the tuberculous process. One patient is in a coma in a nursing home. Three other patients were also in a nursing home due to the consequences of the tuberculous process.
A complete recovery is recorded for 15 patients. Most of these cases are patients with a single abcess in a buttock. All others have some degree of permanent handicap due to the tuberculosis.

VIII.4. Discussion

diagnosis

Most of the patients had a chronic condition for which they sought relief. Most of the patients with tuberculosis were known to have RA. As is shown in Chapter VI there appears to be a relation between RA and TB (9). The onset of RA may occur at any time in life. The peak onset is in the fourth decade (4). Since arthrosis is a disease of the elderly the mean age found is higher. The findings in this cohort on these items are as to be expected.

symptomatology

Malaise is the most frequently scored symptom. Smelt found an equal distribution of general symptomatology (12). General symptomatology is not outspoken, the disease normally has an insidious onset (7). In this cohort weight loss is not the most commonly scored general symptom in patients with extrapulmonary tuberculosis as it is in pulmonary tuberculosis (15).
Pain and swelling are common symptoms in extrapulmonary tuberculosis (10,11).

localisation

Tuberculous arthritis is usually monarticular, and usually affects spine, hips, and knees (7). In the group studied the frequency of tuberculous lesions in the buttocks is remarkable. This localisation could be explained by the administration of multiple injections with steroids and/or phenylbutazone which caused trauma and diminished immunity (8).

tuberculin skintest

In the Netherlands it is a generally accepted that everyone born before 1945 may be considered as having a past primary tuberculous infection. That is the reason why in a considerable part of the cohort no tuberculin skintest was performed. From the age of 50 the tuberculin-index and sensitivity is decreasing which in some cases explain the diameter of the reaction (1) but some other conditions may also cause anergy (14).
In eight cases a skin test of less than 10 mm was recorded at the first survey. In three of these cases a conversion of the test was observed (born respectively in 1939, 1955 and 1924).

diagnosis

In most cases both the examination of a spontaneously produced specimen of sputum by smear (Ziehl-Neelsen) and the culture were positive. The diagnosis of tuberculous arthritis should be confirmed by a positive culture from synovial fluid or tissue.

therapy

As is shown in Chapter VI there was a considerable delay between the first symptoms and the moment of diagnosis (9). In 14 cases there was no suspection of tuberculosis even after a first incision of the abcess, confirming other reports on doctor's delay in the treatment of tuberculosis (3). The frequency of side-effects is as expected (6).

hospitalisation

The healing stage with restoration of bony tissue and resorption of the abscess takes about two years after medicamentous treatment has started (13). Rehabilitation of a patient with bone and joint tuberculosis is a long and costly process.

results

Each case in this cohort has it's own history. Fifteen patients recovered completely. The rest of the cohort became handicapped and four of them died because of the tuberculosis. Despite modern chemotherapeutic measures and modern surgical techniques extrapulmonary tuberculosis is a serious disease with a prognosis related to the localisation, the extent of the disease and other concommitant diseases.

VIII.5. References

1. Bleiker MA. Tuberculine en tuberculineonderzoek VI.18 Leerboek der tuberculosebestrijding. 's-Gravenhage: Koninklijke Nederlandse Centrale Vereniging tot bestrijding van tuberculose, 1984.
2. Geneeskundige Hoofdinspectie van de Volksgezondheid afdeling infectieziekten. Rapport aan de Geneeskundig Inspecteur van de Volksgezondheid voor Noord Brabant inzake de explosie van voornamelijk extrapulmonale tuberculose bij patienten in behandeling bij een arts in Veghel. 1990; januari Rijswijk.
3. Geuns H van. Organisatie en praktijk van tuberculosebestrijding VII.12 Leerboek der tuberculosebestrijding. 's-Gravenhage: Koninklijke Nederlandse Centrale Vereniging tot bestrijding van tuberculose, 1984.
4. Gilliland BC, Mannik M. Infectious arthritis in: Principles of internal medicine. 1974 McGraw-Hill Book Company New York.
5. Girdlestone GR. Tuberculosis of bone and joint. 1965 Oxford University Press, Oxford.
6. CMPC. Farmacotherapeutisch Kompas 1993 Ziekenfondsraad Amstelveen.
7. Newton P, Sharp J, Barnes KL. Bone and joint tuberculosis in Great Manchester 1969-79 Ann Rheum Dis 1982;41:1-6.
8. Offerhaus L. De russische roulette van de pyrazolonen. Ned Tijdschr Geneeskd 183 ;127(15):638-42.
9. Postema CA, Bilkert-Mooiman MAJ, Heesbeen K, et al. Een explosie van voornamelijk extrapulmonale tuberculose in een artsenpraktijk. Ned Tijdschr Geneeskd 1992;136(50):2475-80.
10. Probst FP, Bjorksten B, Gustavson KH. Radiological aspects of chronic recurrent multifocal osteomyelitis. J Bone Joint Surg (Br) 1980;62: 376-80.
11. Reinhard W. Die Tuberkulose der Knochen und Gelenke. 1966 Springer, Berlin Heidelberg New York.
12. Smelt AHM, Roldaan AC, Furth R van. Pulmonale en extrapulmonale vormen van tuberculose; klinische ervaringen in de tachtiger jaren. Ned Tijdschr Geneekd 1989;133(2):66-70.
13. Thijn CJP, Steensma JT. Tuberculosis of the skeleton. Springer Verlag 1990 Berlijn.
14. Veen J. Aspects of temporary specific anergy to tuberculin in Vietnamese refugees. Thesis 1992 University of Groningen. The Netherlands.
15. Warns EHJ. Syllabus skelettuberculose. KNCV 1979 The Hague.

IX. Extrapulmonary tuberculosis caused by a possible relation between a pulmonary infection with M.tuberculosis and trauma.

IX.1. Introduction

As described in the previous Chapters, a cause of the "Veghel explosion" might be an exogenous respiratory infection with a secondary haematogenous spread to a locus minoris resistentiae. A recent pulmonary infection can spread via alveolar macrophages that are deposited elsewhere in the body and are killed locally and in this way cause extrapulmonary tuberculosis at the site of a blunt trauma (14). In a well-documented case, Stead describes the time interval in which a tuberculous chest-wall abscess developed after a blunt trauma and a preceding (silent) primary tuberculous infection.

Exogenous reinfection is quite unusual in the Netherlands because of the very low infection incidence. Nevertheless there are some predisposing factors for this mode of transmission in the "Veghel explosion" (6,12) The chance of exposure to *M. tuberculosis* in the practice was exceptionally high in comparison to the general population.

Blacklock et al. (2) used a model in rabbits and guinea-pigs, in which they produced a primary lung lesion and studied the haematogenous spread of the bacilli. Insertion of silk threads through muscular tissue at widely separated places one, two three and four weeks after the inoculation caused the development of secondary tuberculous lesions only around the threads that were inserted in the fourth week after inoculation. They concluded that the factor time was very critical: the spread of the infection by the blood-stream was taking place shortly before the twenty-eight day after inoculation. This phenomenon may also explain what happens in man with regard to the occurrence of extrapulmonary tuberculosis, for though all forms of trauma are frequent they should happen in a certain time-period. This can also explain for instance why tuberculosis of the knee occurs more frequently in young adults where trauma due to sport activities happen more frequently than in other age groups. For such secondary lesions to occur the time factor, as stated by Blacklock, is all important. There must be bacteriaemia at the moment that the local injury takes place; how often this occurs in men is unknown.

For most patients in the "Veghel cohort" the time interval between their last actual active contact with *Mycobacterium tuberculosis* was at least several decades ago. Memory could be diminished (3). It should also be taken into consideration that treatment with corticosteroids diminishes the immunological resistance.
A joint which has been traumatised by an injection during an actual pulmonary infection is predisposed for infection, as several experiments and observations

have shown (2,10). RA itself also predisposes for a septic arthritis (4). This sort of pathogenesis fits very well with some unsolved explosions in history (9,15) and with some case-reports (5,7,8,11) of extrapulmonary tuberculosis in the literature in which the same kind of pathogenesis was suggested.

By analysing the data of the "Veghel cohort" there were some patients in whom the history was very specific and precise. It was suggested that there might be a possible time relation between a visit on a "positive" day, the administration of an injection and the first appearence of the extrapulmonary infection. This idea was later reinforced by the experimental results of Blacklock.

IX.2. Materials and methods

As described in Chapter VI in 1988, the tuberculosis-units of the municipal health services were asked to examine the patients who were known to visit the doctor's practice in Veghel and that were inhabitants of the unit's region.
Together with the radiological follow-up as described in Chapter VII, an evaluation form was send to the units with a number of questions concerning specific missing data of the patients in relation to their tuberculosis.
The clinics were asked to complete the data and to return the form.
The patients had given informed consent.
All the records of the patients were re-analysed and all visits that had been made to the practice were documented as "positive" or "negative" visits. Visits to the practice on days that one of the six patients visited the practice in the period that they were contagious were designated as "positive" days.
In the same way all the injections that were administered were recorded individually per patient.
Finally an analysis of the history with regard to the probable first week of illness due to the tuberculous process was made.
Because most patients had several injections on different occasions and also had had several contacts, all the possible combinations of these three items (contact, injections, symptoms) were made retrospectively from the probable first week of illness.

IX.3. Results

The total cohort studied consisted of the 55 patients described in Chapter VI.

Of 13 patients with extrapulmonary tuberculosis the data were so specific and the history was so well documented that their first week of illness could be indicated with a high degree of certainty.

Table IX.1. Time relation (in week numbers) between a possible contact, the administration af an injection and the first symptoms in 13 patients with a well-documented history of extrapulmonary tuberculosis.

patientnumber	contact	injection	symptoms
001	23	26	37*
	30	35	37
	23	30	37
	23	35	37
010	12	16	22*
	16	20	22
015	6	13	17
	10	13	17*
020	44	48	53*
028	14	16	31
	14	18	31*
	14	20	31
	14	22	31
	14	24	31
	14	27	31
	14	29	31
029	22	25	41
	22	27	41
	22	30	41
	25	27	41
	25	30	41*
	25	33	41
035	35	44	48
	39	44	48*
	39	47	48
	41	44	48
	41	47	48
036	16	25	30
	25		30**

patientnumber	contact	injection	symptoms
037	50	3	13*
	50	8	13
	50	9	13
	50	12	13
039	14	18	30
	14	20	30
	14	27	30
	14	28	30
	16	18	30
	16	20	30*
	16	27	30
	16	28	30
	18	20	30
	18	27	30
	18	28	30
051	49	52	8
	49	1	8*
	49	2	8
	49	3	8
	49	4	8
	49	5	8
053	39	42	47*
	39	44	47
054	14	18	25
	14	20	25
	14	22	25
	14	24	25
	16	18	25
	16	20	25*
	16	22	25
	16	24	25

* Most probable combination

** Within 24 hours erysipelas with subsequent TB in the same joint

Taking into consideration the findings of Blacklock, the most probable combination was thought to be the one which differed least from the 28 day interval between the inoculation and the injection. Graphically the relation between the three items is demonstrated in figure IX.1.

The average interval between the contact and the injection is four weeks (range 3-5) and the interval in weeks between the contact and the first symptoms of the extrapulmonary proces is 11.5 weeks (range 7-17).

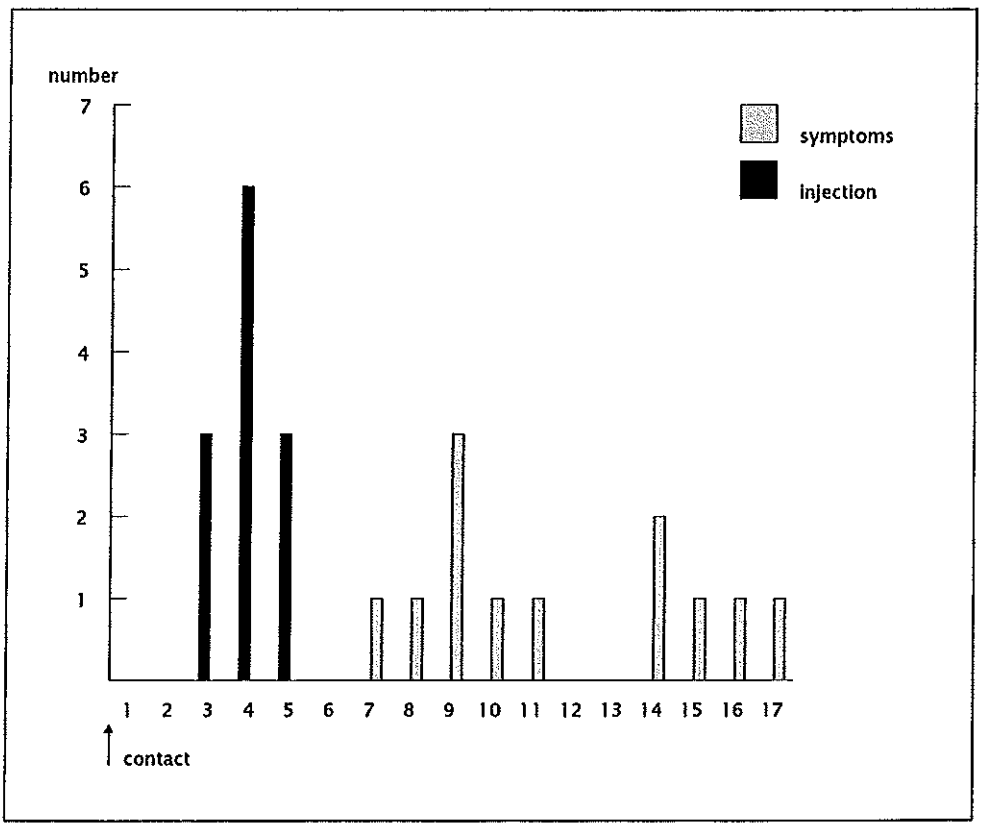

Figure IX.1. The interval in weeks between a possible contact with a contagious tuberculosis patient, an injection and first symptoms of extrapulmonary tuberculosis.

IX.4. Discussion

The data presented here suggests that a relation between the three items indeed exists. Nevertheless it must be taken into consideration that these data are selective, the method is uncontrolled and the study is in retrospect and based on clinical impressions.
It was not possible to form a appropriate control group. Based on the data of bacterial cultures and RFLP a single cause of the "Veghel explosion" is most likely. The dates of contact presented are assumed to be the ones at which the infection was transmitted. Most patients had many visits on positive days and there is no definite proof that infection was transmitted on that specific moment.
On the other hand these findings do confirm the many case histories of different authors (1,8,9,11,13,14). Stead (14) describes the time interval in which a tuberculous chest-wall abscess developed after a blunt trauma and a preceding (silent) primary tuberculous infection. Especially this well-documented case is quite illustrative for the interval between the contact en the first symptoms.
Blacklock (1) described three cases of tuberculous abscesses occurring at the site of penicillin injections. He thought them to be caused by haematogenous spread from a known tuberculous process elsewhere.
Heycock (9) described four young patients in whom tuberculous lesions of muscle followed injections of penicillin. It was subsequently discovered that a nurse at the hospital had developed open pulmonary tuberculosis and that she had given some of the injections to each of the four infants.
Sikl (13) described four cases of extrapulmonary tuberculosis at the site of penicillin injections. The source of infection could not be discovered.
Forbes (8) describes a case of tuberculous abscess developing deeply in the thigh at the site of previous penicillin injections. He strongly advocates the theory that the cause of this abscess was a haematogenous spread from a focus elsewhere.
Hounslow (11) describes two patients admitted to his hospital with lupus verrucosus of the hand following an injury involving a breach of skin surface. Both patients had active pulmonary lesions. He suggested a haematogenous spread to a locus minoris resistentiae. He also referred to the well-known association of injury with other tuberculous conditions such as tuberculosis of joints.

IX.5. Conclusion

There appears to be a causal relation in time between a possible contact with a patient with contagious tuberculosis of the lung, the administration of an injection and the first symptoms of extrapulmonary tuberculosis. If an injection is administered four weeks after a contact with a patient with contagious tuberculosis one has to take into consideration the appearence of symptoms of extrapulmonary tuberculosis after an average of 7.5 weeks. These data have been confirmed in animal experiments (2) and are consistent with several case reports (5,7,8,9,11,13,14).

IX.6. References

1. Blacklock. Injury as an etiological factor in tuberculosis. Proc Roy Soc Med 1956;50:61-8.
2. Blacklock JWS, Williams JRB. The localisation of tuberculous infection at the site of injury. J Bact Path 1957;74:119-31.
3. Bleiker MA. Tuberculine en tuberculineonderzoek VI.18 Leerboek der tuberculosebestrijding. 's-Gravenhage: Koninklijke Nederlandse Centrale Vereniging tot bestrijding van tuberculose, 1984.
4 Brewerton DA. Causes of arthritis. Lancet 1988;ii:1063-5.
5 Coope PJ. Tuberculous abscess formation following penicillin therapy. Proc R Soc Med 1947;40:161-2.
6. Douma J. Tuberculose als ziekteproces bij de mens. V 42 VII 23. Leerboek der tuberculosebestrijding. 's-Gravenhage: Koninklijke Nederlandse Centrale Vereniging tot bestrijding van tuberculose, 1984.
7. Ebrill Elek SD. Tuberculous abscess formation following intramuscular penicillin. Lancet 1946;ii:379-80.
8. Forbes GB, Srange FG. Tuberculous abscess at the site of penicillin injection. Lancet 1949;i:478-9.
9. Heycock JB, Noble TC. Four cases of syringe transmitted tuberculosis. Tubercle 1961;42:25-7.
10. Hortas C, Ferreiro JL, Galdo B, et al. Tuberculous arthritis of peripheral joints in patients with previous inflammatory rheumatic disease. Br J Rheumatol 1988;27:65-7.
11 Hounslow AG. Tuberculous abscess at the site of injection. Lancet 1949;i:709.
12. Nardell E, McInness B, Thomas B, et al. Exogenous reinfection with tuberculosis in a shelter for the homeless. N Engl J Med 1986;315:1570-5.
13. Sikl H. Extravisceral Tb primoinfection after injections of penicillin. Cas.Lek. Cesk 1950;935-7.
14. Stead WW, Bates JH. Evidence of a "silent" bacillemia in primary tuberculosis. Ann Int Med 1971;74:559-61.
15. Tamamura M, Ogawa I, Amano S. Observations on an epidemic of cutaneous and lymphatic tuberculosis which followed the use of anti-typhoid vaccine. Am Rev Tub Pulm Dis 1955;71:465-72.

X. *Summary*

In this thesis the result of an epidemiological analysis of an explosion of predominantly extrapulmonary tuberculosis is reported. Because of some uncertainties concerning the pathogenesis of extrapulmonary tuberculosis a cohort-follow up study was performed.

In Chapter I the introduction and the aim of this study is presented.

In Chapter II the normal joint is described. Different aspects of acute and chronic arthritis are reviewed. Some aspects of bacterial arthritis are discussed in general and special reference is given to tuberculous arthritis.

In Chapter III the immunological, pathological and clinical pattern of extrapulmonary tuberculosis is discussed. Attention is focused on tuberculous arthritis.

Chapter IV reviews the relation between rheumatoid arthritis and tuberculosis. Details of historical and more recent research that have relevance for the above-mentioned explosion are discussed in more detail. A model is constructed for the suggested relation between chronic arthritis and infection in general and for the relation in the case of tuberculosis in particular.

Chapter V is focused on the specific chest radiography patterns of tuberculosis and rheumatoid arthritis.

In Chapter VI the explosion of predominantly extrapulmonary tuberculosis in a general practice is described. This outbreak of predominantly extrapulmonary tuberculosis (TB) occurred in a group of about 550 patients with rheumatoid arthritis (RA). These patients had been attending the practice of a former general practitioner who treated cases of rheumatoid arthritis with phenylbutazone and steroids. The number of diagnosed tb cases was 55. Six cases had during the period in which they visited the practice a contagious lung localisation. The possible sources of the outbreak were analysed. Both a visit on a same day as a sputum positive patient (χ^2 trend: 20.4; $p < 0.001$) and the administration of steroids (odds ratio (OR): 36.2; 95% confidence interval (CI): 8.8-313) were independent risk factors. There also appeared to be a relationship between TB and RA (OR: 4.4; 95% CI 2.2-9.1). Exogenous re(infection) and endogenous reactivation are possible causes of this outbreak.

In Chapter VII the aim of the cohort follow-up study is explained. The hypothesis is formulated that in this cohort it is possible to demonstrate changes on a chest X-ray made approximately four years after the explosion in comparison with the one made during the national survey. Because lunglesions which had developed after the first examination in 1988 might point to a recent infection a second roent-

genographic examination was performed four years after the explosion in patients who had been treated for extrapulmonary tuberculosis. No signs of a recent pulmonary infection with *M. tuberculosis* were found in those patients. This means that no support for a recent pulmonary infection which might have been the focus for the haematogenous spread of *M. tuberculosis* to extrapulmonary sites was obtained. This result however does not exclude such a mechanism.

The findings and the consequences of this study are discussed in more detail. Clinical data on the course of the disease were collected and analysed and presented in Chapter VIII.

Finally some other data with regard to the possible relation between a recent pulmonary infection and an extrapulmonary process of the "Veghelcohort" are presented in Chapter IX.

XI. Samenvatting

In dit proefschrift worden de resultaten van een epidemiologische analyse van een explosie van voornamelijk extrapulmonale tuberculose weergegeven. In verband met onduidelijkheid over de pathogenese van deze gevallen van extrapulmonale tuberculose werd een cohort follow-up studie uitgevoerd.

In hoofdstuk I wordt het onderwerp van dit proefschrift ingeleid en wordt het doel van het onderzoek uiteengezet.

In hoofdstuk II wordt het normale gewricht beschreven. De verschillende aspecten van acute en chronische gewrichtsontsteking worden toegelicht. Op de aspecten van bacteriële gewrichtsontsteking in het algemeen en van tuberculeuze gewrichtsonsteking in het bijzonder wordt nader ingegaan.

In hoofdstuk III worden de immunologische, de pathologische en klinische eigenschappen van extrapulmonale tuberculose belicht. De nadruk ligt hierbij op tuberculeuze gewrichtsontsteking.

In hoofdstuk IV wordt ingegaan op de relatie tussen reumatoïde arthritis en tuberculose. Gegevens uit onderzoek van wat oudere datum en recente onderzoekgegevens die van belang zijn in het kader van bovengenoemde explosie worden besproken. Tevens wordt een model gepresenteerd voor de relatie tussen chronische gewrichtsontsteking en infectie in het algemeen en voor het samenhang met tuberculose in het bijzonder.

Hoofdstuk V gaat in op de verschillende aspecten van het beeld van het röntgenologisch borstonderzoek bij tuberculose en reumatoïde arthritis.

In hoofdstuk VI wordt een explosie van voornamelijk extrapulmonale tuberculose beschreven. In de praktijk van een arts die vooral patienten met reumatoïde arthritis behandelde met fenylbutazon en parenterale corticosteroïden deed zich vanaf 1987 een explosie voor van voornamelijk extrapulmonale tuberculose. In totaal werd bij 55 patienten van de ongeveer 550 tellende praktijk actieve tuberculose geconstateerd. Bij 6 van hen was ten tijde van het bezoek aan de praktijk sprake van een besmettelijke vorm van longtuberculose.

De belangrijkste risicofactoren die met deze besmetting samenhingen, waren het toegediend krijgen van corticosteroïden (odds ratio: 36,2;95%-betrouwbaarheidsinterval: 8,8-313) en het bezoek aan de praktijk op een dag dat ook een patiënt met een besmettelijke tuberculose deze bezocht (χ2-trend: 20,4; $p < 0,001$).
Er was ook een verband tussen tuberculose en RA (odds ratio: 4,4; 95 % betrouwbaarheidsinterval: 2,2-9,1). Tot de mogelijke oorzaken van deze explosie behoren exogene (her) infectie en endogene reactivatie.

In hoofdstuk VII wordt het doel van het cohort vervolgonderzoek uiteengezet. De hypothese luidt dat er in dit cohort op de thoraxfoto die ongeveer vier jaar na de explosie genomen werd, veranderingen zichtbaar zijn die bij het eerste onderzoek ten tijde van de explosie niet aanwezig waren. Omdat longafwijkingen die ontstaan zijn na het eerste onderzoek kunnen duiden op een recente infectie werd het tweede röntgenonderzoek vier jaar na de explosie verricht bij patiënten die behandeld waren in verband met extrapulmonale tuberculose. Er werd bij deze patiënten geen recente infectie met *M. tuberculosis* gevonden. Al met al werden er geen aanwijzingen gevonden voor een recente longinfectie van waaruit *M. tuberculosis* naar een extrapulmonale localisatie was uitgezaaid. Dat betekent evenwel niet dat een dergelijke ontstaanswijze van extrapulmonale tuberculose is uitgesloten.
De onderzoekgegevens en de daaraan te verbinden conclusies worden nader besproken.

Een aantal gegevens in het kader van diagnostiek en behandeling van de ziekte werden verzameld en deze zijn weergegeven in hoofdstuk VIII.

Tenslotte worden in hoofdstuk IX een aantal andere gegevens met betrekking tot de mogelijke relatie tussen een recente (long)infectie met tuberculose en een extrapulmonale localisatie van tuberculose geanalyseerd.

Dankwoord

Mijn dank gaat in de eerste plaats uit naar mijn promotor, Prof.dr. J.Huisman. Joop, ik vind het een eer om een van je promovendi te zijn en ik dank je voor je geduld en toewijding. Je bent in de achterliggende jaren een steun en toeverlaat voor mij geweest.

De hooggeleerden Hilvering, van der Maas en van de Putte wil ik bedanken voor bereidheid tot deelname aan de promotiecommissie.

Het resultaat van de hier gepresenteerde studie is tot stand gekomen dankzij de inzet van velen. Heel in het bijzonder wil ik de medewerkers van de consultatiebureaus voor tuberculosebestrijding in Nederland bedanken voor hun bereidwilligheid mee te werken aan deze studie. Een speciaal woord van dank aan de collegae Mw. J.C.H.M. Schepp-Beelen en Mw. J.J. Heij en de medewerkers van de afdeling tuberculosebestrijding van de GGD Den Haag voor het onbevooroordeeld lezen en verzorgen van de foto's.

De collegae T.L. Mellema en Mw. J.A.C.M. Année-van Bavel wil ik danken voor hun adviezen met betrekking tot de opzet van de formulieren.
Dr. J. Veen wil ik bedanken voor de vele verhelderende en stimulerende discussies die wij hadden over de hier gepresenteerde studie. Een soortgelijk woord van dank aan Dr.M.A. Bleiker voor zijn wijze adviezen speciaal met betrekking tot de hypothesevorming. Ook Mw. J.T.Steensma, longarts en Dr.D.G. Groothuis past een woord van dank. Zij gaven vaak en goed gefundeerd weerwoord en wij hebben dan ook menig "wetenschappelijk robbertje" geknokt. Dr.L.H. Lumeij en H. Houweling, arts wil ik in verband met de door beiden gegeven epidemiologische adviezen niet onvermeld laten.

Voor de literatuurverzameling is een woord van dank op zijn plaats voor H. Westra en W. Vlaardingerbroek van de WVC bibliotheek en H. Ultée en Mw. M. van Amsterdam van het secretariaat van de Ziekenfondsraad.

De medewerkers van de Geneeskundige Inspectie Noord-Brabant en van de afdeling Infectieziekten van de Geneeskundige Hoofdinspectie waren vanaf het begin zeer behulpzaam bij het verkrijgen van de noodzakelijke gegevens en bij het opstellen van de tabellen.

Collega N.T.M. Jack, anesthesioloog wil ik bedanken voor de controle op taalkundige onjuisheden.

Een speciaal woord van dank aan al diegenen die bij mijn vorming een rol hebben gespeeld. In het bijzonder wil ik hier noemen mijn ouders, Prof.dr.W.F.B. Brinkman bij wie ik mijn KNO opleiding volgde, Prof.dr.R.Th.R. Wentges die bij mij weten-

schappelijke belangstelling aankweekte en Drs.B.F. Groothuis van de St.Ziekenhuisvoorzieningen Oost-Achterhoek die mij onder moeilijke omstandigheden steunde en stimuleerde door te zetten.

Mijn oud hoofd van dienst bij de Geneeskundige Inspectie van de Volksgezondheid voor Noord-Brabant J.W. Schaper dank ik voor het vertrouwen dat hij in mij stelde om deze zaak te behandelen en in zijn stimulerende rol om te promoveren. Dr.H. Bijkerk en wijlen Dr.H van Geuns stimuleerden mij eveneens in die richting en zij hadden bij nacht en ontij steeds een luisterend oor en constructieve ideeën.

Ik ben de KNCV erkentelijk voor de bijdrage in de uitgave van dit proefschrift.

Mijn collegae van het Medisch Advies College (hoofd: A. Boer, arts) van de Ziekenfondsraad wil ik danken voor de prettige samenwerking in de achterliggende periode. Mede door hun souplesse kon ik dit proefschrift schrijven. Mw. S. Cicilia-Hinds en R. de Jongh dank ik in dit verband voor hun medewerking bij de logistieke zaken. De Algemeen Secretaris van de Ziekenfondsraad E. Brouwer en de medewerkers van de afdeling Externe Betrekkingen en de huisdrukkerij van de Ziekenfondsraad ben ik dank verschuldigd voor de medewerking bij de uiteindelijke totstandkoming van deze dissertatie.

Curriculum Vitae

The author was born on June 14th 1951 in Eindhoven. After graduation from the Eindhoven Protestant Lyceum (HBS-B) in 1969 he studied at the Medical Faculty of the Free University in Amsterdam.

After completing his medical studies in 1977 he started his training in ENT in the department of Ear-Nose-Throat-surgery (head Prof.Dr. W.F.B.Brinkman) of the University Hospital St. Radboud in Nijmegen. In this period he performed a study on Rhinomanometry.

From 1980 until 1984 he was ENT consultant in the hospitals of "The Hospital Foundation Oost-Achterhoek" in Winterswijk. During these years he held several positions in the medical staff of the Foundation. He was also active in some political and social committees.

In 1984 he was appointed by Her Majesty The Queen of the Netherlands as a Regional Officer of Health in the province North-Brabant. In this period he was active in public health in general and care for the elderly in particular. He also was an adviser to the provincial authorities concerning the cadmium-pollution of the region "De Kempen".

In august 1988 he started the official investigation on the subject of this study. In october 1988 he was appointed as Medical Officer for Infectious Diseases in the Department of the Chief Medical Officer in Rijswijk. Amongst other problems in this period he had to deal with Meningococcal disease and foodborn problems related with Salmonella Enteritidis. He was member of some expert committees of the World Health Organisation and adviser to several committees of the Dutch Health Council.

In 1989 he was registered as a Public Health consultant.

From 1990 onwards he is medical adviser to the Dutch Health Insurance Council. He is chairman of the expert committee of the Registration Commitee for Medical Officers of the Royal Dutch Medical Association and member of the scientific board of the Dutch Influenza Foundation and the Dutch Incontinence Foundation. He has published a number of papers on different subjects in several medical journals.