Yersinia Enterocolitica Infection in Norway

YERSINIA ENTEROCOLITICA INFECTION IN NORWAY

A study on prevalence, epidemiology, and acute and chronic manifestations.

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INTRODUCTION

History

The genus Yersinia of the family Enterobacteriaceae includes three well-established human pathogens (Y. pestis, Y. pseudotuberculosis, and Y. enterocolitica), and several non-pathogens (1, 2).

Y. pestis, the causative organism of the bubonic plague was isolated by Alexandre Yersin, in 1894 (3). Since antiquity, this microorganism has caused four great pandemics. The 14th. century pandemic (the Black Death) may have killed a third of Europe's population; in Norway as much as 40-50% of the population may have died (4).

Y. pseudotuberculosis (described 1884) causes epizootic disease, especially in rodents, with necrotizing granulo matous disease of liver, spleen and lymph nodes. In humans it may cause acute abdominal disease, septicemia, arthritis and erythema nodosum (5, 6).

Y. enterocolitica (Bacterium enterocoliticum) was first described by Scleifstein a nd Coleman (USA) in 1939 and 1943 (7, 8). Only a few isolations were reported during the following years, and these were labelled differently, as the species was as yet unclassified. In Europe, the microorganism was isolated from two patients who died of generalized infection with liver abscesses, in 1949 (9). In 1964, it was isolated from a patient who underwent surgery because of acute terminal ileitis (10), and the same year the species name Yersinia enterocolitica was

proposed. During the following years, it was isolated from humans with gastrointestinal disease in many countries , most frequently in cooler climates (1, 11).

Description

Y. enterocolitica is a facultative anaerobic, Gram-negative asporogenic rod that exhibit s significant pleomorphism. It has been classified into approximately 70 serogroups on the basis of O antigens (12) The strains pathogenic for man and animals belong to only a few serogroups, and show distinct serogroup-biovar-phagevar combinations (1). The serogroup-biovar combinations commonly involved in human disease are O:3 biovar 4, O:9 biovar 2, O:8 biovar 1B, and O:5,27 biovar 2. Serogroup O:3 is the most frequently encountered in Europe, followed by O:9. In Norway, almost exclusively serogroup O: 3 (biovar 4, phagevar Vlll) is encountered.

Y. enterocolitica is able to multiply at temperatures approaching 0 o C, it can grow in properly refrigerated foods, and survive in frozen foods for long periods (13).

Y. enterocolitica requires iron for growth, but is unable to synthesize iron-binding substances (siderophores), and in consequence must obtain them from other bacteria or host tissue (14). Normal human tissue iron concentrations are growth-limiting, but individuals with iron overload are prone to acquire disseminated infections (15, 16, 17, 18, Notice

ADDENDUM - 172).

Human serum is bactericidal against Y. enterocolitica (19); heating the serum at 56 o C abolishes the killing, indicating involvement of complement (20).

The essential pathogenic factors of Y. enterocolitica are its abilities to invade animal cells, and to multiply within animal cells, even in macrophages (21, 22). The pathogenic serogroups of Y. enterocolitica harbour a plasmid (small extrachromosomal piece of DNA) 40-50 megadaltons in size, which encodes a series of proteins, several of which are important virulence factors (22).

Many strains of Y. enterocolitica produce a heat-stable enterotoxin when

cultured at 25 o C (23); and some strains even at refrigeration temperatures of 3-6 o C. (24). The enterotoxin is not produced at normal body temperature, neither under anaerobic conditions; its relevance in diarrheal disease has therefore been doubted (25).

Reservoir and transmission

Y. enterocolitica is considered to be a food-borne pathogen, but only during a few outbreaks (one in Europe) has it been isolated from suspected food sources (26, 27). The pig is the only animal consumed by man which regularly harbours pathogenic Y. enterocolitica (28), and its occurrence in pork product may have been underestimated (29, 27). A high percentage of Norwegian slaughter pigs are healthy carriers of serogroup O:3 (30).

Firm evidence for transmission by consumption of contaminated water is lacking (28, 31), but consumption of untreated water has recently been identified as a risk factor for infection (27). Contamination of donor blood with Y. enterocolitica may represent a hazard in blood transfusion (32).

Diagnosis of Y. enterocolitica infection

During the first days or weeks of the acute infection, Y. enterocolitica may be isolated from stools of most patients presenting with diarrhea, or from mesenteric lymph nodes of patients w ho are subject to laparotomy (25, 33). However, a substantial part of patients with acute infection do not present enteritic symptoms. In these, as in patients with chronic disease, diagnosis must rely on demonstration of a significant antibody response against the micro organism. For this purpose, tube agglutination has been widely used in the Nordic countries. This method may be complicated by the existence of cross-reacting antigens (25, 34, 35), but the reported cross-reactions have largely been attributed to serogroups other than O:3, which has been recognized as immunologically specific (36).

Other methods including enzyme-linked immunosorbent assays (ELISA) and radioimmunoassays (RIA) are now available (34).

Clinics

Acute manifestations of the Y. enterocolitica infection like abdominal pain and diarrhea, mesenteric lymphadenitis / regional ileitis (5, 10, 37), arthritis or erythema nodosum (5, 38, 39), and fulminant disease and septicaemia in patients with debilitating diseases (9, 15) have been recognized for twenty-five years. The most common acute manifestation may be a self-limited gastroenteritis, especially in children (25, 40). The scope of the infection's manifestations has steadily been extended, thus hepatic (5, 15, 39), pancreatic (41, 42), renal (39, 43), cardiac (5, 38, 39, 44, 45, 46), venous (47), pulmonary (48, 49), eye (5, 50), neurologic (5, 51, 52), or thyroid (53) involvements, spontaneous abortion (5), conditions resembling sarcoidosis (54), and adverse effect of iron (16, 17) have been reported.

In Norway, Y. enterocolitica is the cause of considerable morbidity. During 1982-1991, a total of 1958 bacteriologically verified cases were recorded by the Norwegian national surveillance system. A case-control study, performed in the Oslo region during the period October 1988 through January 1990, detected an incidence rate of 6.4 bacteriologically confirmed cases/100.000 population/year. Approximately 90% of the cases had acquired the infection in Norway, and more than 95% of the infections were caused by serogroup O:3, biovar 4 (40). Chronic manifestations. Clinical follow-up studies have documented that ankylosing spondylitis may develop subsequently to Y. enterocolitica infection, especially in patients presenting the histo compatibility antigen HLA-B27 (55, 56). An association between Y. enterocolitica infection and rheumatoid arthritis has further been suggested (57, 58).Regarding abdominal disease, several previous reports claim that sustained or recurrent diarrhea or abdominal pain may follow the acute Y. enterocolitica infection (5, 59, 60, 61). An association with chronic colitis or ulcerative colitis (UC) was suggested from clinical observations twenty years ago (38, 62), later were high frequencies of specific antibodies observed among patients with UC (58) and Crohn's disease (CD) (63). In 1977, clinical

observations made me suggested the possibility of chronic liver involvement (64), and during the following years reports of granulomatous hepatitis were added (65, 66, 67).

Recently, virulent Y. enterocolitica has been identified by immuno fluorescent techniques in YERSINIA ENTEROCOLITICA INFECTION IN NORWAY Dr.med. ARVE SAEBO ISBN 82-7788-017-0INTRODUCTION

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AIMS OF THE PRESENT STUDY

Through a study on 755 Norwegian military recruits (To assess the prevalence of antibodies to Y. enterocolitica O:3 among healthy young Norwegians, and to observe possible regional differences in prevalence.

(To identify risk factors associated with antibody activity to Y. enterocolitica.

(To study possible associations between particular clinical complaints and antibody activity to Y. enterocolitica, as between previous appendectomy and anti body activity. Through follow-up study on 458 hospitalized patients

(To further study frequency, clinical course and mutual relationship of acute and chronic clinical manifestations known to be associated with the Y. entero colitica infection.

(To possibly describe previously unknown acute or chronic clinicalmanifestations associated with Y. enterocolitica infection.(To observe possible immunological aberrations associated with Y.entero-colitica infection, and estimate their relationship to clinical disease.

(To study the influence of the Y. enterocolitica infection on long timesurvival, and describe clinical conditions associated with death.

METHODOLOGICAL CONSIDERATIONS

Material 1

In a small country like Norway, with obligate military service, military recruits constitute a population well suited for medical research, especially prevalence and analytic epidemiological studies. The study was conducted at the Norwegian naval training camp in south western Norway. Among 791 recruits who were enrolled for their obligate service in January 1987, 755 (95%) participated in the study. The 755 recruits were all healthy Norwegian males of approximately the same age (19-26 years old). They represented all districts of Norway, different socio-economic classes, and different previous exposures. Blood samples for evaluation of antibody response to Y. enterocolitica were obtained from all 755 recruits within seven days after they entered the camp. In the meantime, there had been no outbreak of gastroenteritis in the camp. Within two weeks, the recruits answered a standardized questionnaire covering:

(i) demographic data,
(ii) specific exposures, and
(iii)clinical information.

The questions were precise and easily understandable. Information on per operative findings was obtained from hospital case records in 26 of 34 recruits with previous appendectomy.

Material 2.

During the 10-year period 1974-1983, Y. enterocolitica infection was diagnosed in 553 hospitalized patients, by antibody response and/or isolation of the microorganism. Excluded were 95 patients within sufficient or missing hospital files. Adequate clinical information was obtained on 458 patients (202 males and 256 females) admitted to 52 different hospitals, and, dependent on the clinical manifestations, to departments of internal medicine, surgery, orthopaedic surgery, rheumatology, paediatrics, gynaecology and obstetrics, ophthalmology, neurology, pulmonary diseases, and dermatology. The 458 patients constituting the material of the study were followed as a cohort prospectively (in sense of the directional pursuit), from the Y. enterocolitica infection, in order to observe eventual chronic complications. However, the diagnostic methods used in the period 1974-83 were not equal to those presently available. Sophisticated methods for the demonstration of Yersinia in diseased tissues were not accessible, and in many cases the evidence of chronic yersiniosis was circumstantial.

Clinical data were obtained from the various departments upon the first admission, and from all subsequent admissions. Valuable information was also obtained through general practitioners. Records of death were obtained from local registries.

At termination of the study (June, 1987), 46 patients were dead and two could not be located. Of the remaining patients 380/410 (92. 7%) replied to a detailed clinical questionnaire, concerning development of chronic conditions that might be attributable to yersiniosis, and recent medical assistance or hospital admission. In case of 12/30 patients who did not answer the questionnaire we have complete hospital records, therefore the final clinical information is missing in only 18/410 patients alive (4.4%).

Selected groups were more closely re-examined:

1) Twenty four patients who had been admitted to Bergen University Hospital underwent a thorough examination including assessment of antibody response to Y. enterocolitica, evaluation of serum levels of complement component, liver function tests, and tests for antinuclear factor (ANA) and rheumatoid factor (RF). Patients with persisting arthralgic complaints were examined for urethritis and for presence of the histo compatibility antigen HLA-B27, and had radiographic examinations of ileosacral and extremity joints.

Patients with severe chronic diarrhea underwent radiographic investigation of the small intestine, duodenoscopy and colonoscopy, and were examined for malabsorption. Patients with elevated liver parameters were examined for liver disease. Complement component levels were compared with those of 32 first degree relatives and 25 unrelated controls, without antibodies to Y. enterocolitica.

2) Special attention was paid to patients with neurological symptoms. These patients were last reexamined in 1991, with estimation of antibody activity to Y. enterocolitica.

3) Several patients admitted to Akershus Central Hospital have been followed for twenty years by the author; some were also included in a previous follow-up study (60).

Totally, the information on the 458 patients of the present study constitute a database of more than 20.000 pieces of information.

The study of clinical yersiniosis requires a large patient population, followed for a period sufficiently long for the development of chronic disease. At present, these demands may be fulfilled only by including patients from several hospitals, and by using a retrospective approach that obviously will carry certain flaws.

In Norway, determination of antibodies to Y. enterocolitica was introduced, in 1972, by the National Institute of Public Health, and for several years performed almost exclusively by the institute's laboratory. Also samples for cultivation were usually admitted to this laboratory. The institute's records therefore constitute a unique entrance to yersiniosis in Norway.

The material is unbiased in the respect that all patients with available hospital record were included. However, a material constituted by hospitalized patients is selective both by nature

and severity of clinical manifestations; the present study in consequence may concern the more serious manifestations of the Y. enterocolitica infection.

The majority of patients were admitted to hospitals in south-eastern Norway; an observation in concert with the regional distribution of IgG antibody activity observed in the prevalence study.

According to the complexity of the material, and to the fact that the data concerning patient entry were documented in the past, it was found impracticable to collect a reliable control material with a corresponding age, sex, and geographical distribution, constituted by individuals definitely without previous infection with Y enterocolitica, and with a sufficiently long follow-up period. However, the death rate of the study population was compared with the national death rate, and the prevalences of UC and diabetes were compared with prevalences observed in previous Norwegian studies. Serum levels of complement components of the Bergen University Hospital patients were compared with those of control groups.

Some of the Akershus Central Hospital patients were compared with patients without antibodies to Y. enterocolitica in a previous follow-up study (60).

Clinical subgroups of the material were compared with each other, and with themselves over time.

Laboratory techniques

Diagnosis of Y.enterocolitica infection:

During the epidemiological study, diagnosis was based on an enzyme-linked immunosorbent assay (ELISA) using lipopolysaccharide extracted with hot phenol water as antigen (72). Net absorbance values (absorbance in the sample minus the absorbance in the negative control) of (0.1 were regarded as significant. A net absorbance of (0.5 or an increase in the activity of at least 30 % in two consecutive serum samples, was considered indicative of actual or recent infection. The method has been described in Paper l. In addition to IgG activity, serum samples were also examined for IgM and IgA activity.

During the clinical study, diagnosis of Y. enterocolitica infection was based on the following methods:

a) isolation of Y. enterocolitica from fecal samples, and/or
b) antibody response to Y. enterocolitica as evaluated by one of the following methods:

i) bacterial whole cell agglutination using alcohol treated bacterial cells as antigen. An agglutination titer of (640, or a four-fold or greater increase of the titer in two consecutive samples, was recognized as indicative of an actual or recent infection (1974 -1982).
ii) ELISA as described above. Serum samples were examined for both specific IgG and IgM activity. (1982 -1983).

Complement components C3, C4, C3 activator and C1-INH (C1 esterase inhibitor) were quantitated using single radial immunodiffusion with commercial plates purchased from Behringwerke AG, Marburg an der Lahn, Germany.

Liver function tests were performed with autoanalyzer technique.

Other laboratory and clinical examinations in local hospital s were performed according to standard procedures.

STATISTICAL METHODS

During the epidemiological study, univariate analysis was performed with the computer program Epi Info (Centers for Disease Control, Atlanta,USA).

The significance of differences between groups was assessed using chi-square testing; Fisher's exact test was used when an expected cell value was less than 5. Multivariate analysis on 30.000 data elements, with multiple linear logistic regression was done with the computer program Egret (Statistics and Epidemiology Research Corporation, Seattle, USA). All results were expressed as odds ratios (OR) with 95% confidence intervals (CI) and two-tailed p-values.

During the clinical study, the two-sample Student's t- test, the standard error of differences between two proportions, the chi-square test, and Fisher's exact (all two-tailed) were used for comparison between subgroups of the material. For statistical comparison between observed and expected survival rates was used the log-rank or Mantel-Haenszel test, which is considered a valid test of the null hypothesis that the survival functions of two populations are the same. It is, in some sense, optimal if the difference arises because the mortality rate in one group is a constant multiple of the corresponding rate in the other group (73).

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RESULTS AND GENERAL DISCUSSION

(SUMMARY OF THE PAPERS).

PAPER l.
Saebo A, Kapperud G, Lassen J, Waage J. Prevalence of antibodies to Yersinia enterocolitica O:3 among Norwegian military recruits:

Association with risk factors and clinical manifestations.
Eur J Epidemiol 1994; 10: 749-755.
IgG antibody activity to Y. enterocolitica serogroup O:3 was detected in sera from 7.4 % of the 755 military recruits. The highest prevalence (21.4%) was found among recruits from Oslo city. Because of the material's representative geographical distribution and high compliance, it may give a reliable estimate of the national prevalence of IgG antibodies in this age group,

as of regional differences in prevalence. As the infection may be acquired at all ages, the antibody prevalence may increase with age. Several surveys of the prevalence of antibodies to Y. enterocolitica have been conducted in other European countries, but on different subpopulations, and using a diversity of antigens and serological techniques (74). In consequence, it is difficult to compare these results with previous observations.

In a recent Norwegian study performed in the Oslo region, 1988-1990, an incidence rate of 6.4 bacteriologically confirmed cases/100.000 population/year was observed (40). Taking into account the high incidence observed in the younger age groups of that study, and supposing a stable incidence and persistence of the antibody response, one could still hardly expect to demonstrate any antibody response among the 56 Oslo city recruits (< 0.15 case). However, 12 of them had anti body activity. Regarding children and youngsters, therefore, it may be supposed that only a few per cent of cases with acute Y. enterocolitica infection are diagnosed.

Risk factors associated with IgG antibody activity: The following risk factors were found to be independently associated with IgG activity in logistic regression analysis:

a) receiving drinking water from a private well,
b) being a resident of Oslo city, and
c) living in eastern Norway.

We failed to detect an association between Y. enterocolitica and contact with pigs.

The risk of receiving drinking water from a private well was clearly demonstrated by the Bergen city observations: because of lacking municipal water supply, several small hamlets on the outskirts of the city use private wells with stagnant water. The fact that 3/9 recruits who received water from such wells had antibody response, and only 3/100 with other kinds of water supply, supports previous suggestions of water as a reservoir for the microbe (28, 31, 75), and a recent Norwegian case-control study, which identified consumption of undisinfected water as a risk factor for yersiniosis (27). Y. enterocolitica has been isolated from water in several investigations (31), including five Norwegian studies (76, 77, 78, 79, 80) but the majority of strains recovered belong to avirulent serogroups. Further investigations on the occurrence of virulent Y. enterocolitica need to be undertaken, using more sensitive and specific detection methods like nucleic acid probes or polymerase chain reaction.

Residency of Oslo city, and living in eastern Norway were identified as independent risk factors associated with antibody activity to Y. enterocolitica. These connections can so far not be explained. The case-control study referred to above identified consumption of pork products as a risk factor for yersiniosis, and it was speculated whether eating habits (e.g. eating meat raw or rare) may differ geographically (27). Oslo and eastern Norway may have satisfactory municipal water supply, but it should be noticed that the present study demonstrated no advantage of water disinfection, as regards prevalence of antibodies to Y. enterocolitica. Finished Norwegian drinking water vary considerably from district to district; these differences possibly may be related to the epidemiology of some diseases (81).

Clinical considerations: IgG antibody activity was significantly correlated with previous appendectomy, and with the per-operative finding of mesenteric lymphadenitis. This was not unexpected, as mesenteric lymphadenitis, terminal ileitis, or typhlitis are common manifestations of the acute Y.enterocolitica infection. The right iliac fossa symptoms may necessitate laparotomy because acute appendicitis is suspected (5, 10, 37, 82, 83, 84).

Corresponding frequencies of previous appendectomy were reported by recruits from the eastern and the other districts of Norway, but the eastern district recruit with previous surgery had a significantly higher frequency of IgG antibodies (6/14 > 2/20). According to previous reports, the proportion of patients having appendectomy with Y.enterocolitica in Europe or North America ranges from 3.0 to 9.0 per cent (25); the high frequency of IgG antibody among eastern district recruits operated upon therefore is remarkable.

In the present study, five recruits with previous appendectomy complained of steatorrhea; three of them had antibodies to Y.enterocolitica.

Statistically, however, we failed to detect an association between antibody activity and recurrent diarrhea or persistent joint complaints. Individuals with severe complaints, of course, would not have been enrolled for military training.

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on 458 hospitalized patients. Scand J Infect Dis 1991; 23: 517-527.

This paper give s an extensive survey of acute and chronic disease observed among 458 patients hospitalized with Y. enterocolitica infection.

Acute symptoms: 189 patients presented with uncomplicated arthritis, and 200 with diarrhoea. These manifestations overlapped in 91 patients. 56 patients underwent abdominal surgery. Liver involvement was observed in 54 patients (12%). Renal, cardiac, pulmonary, pancreatic and neurologic involvement were observed with small but significant frequencies (8-16/458 patient = 1.75%-3.5%; SD 0.61%-0.86%), and often as components of multiorgan disease, which was observed in several patients. Other manifestations included erythema nodosum (in 60 patients), iridocyclitis, splenomegaly, deep venous thrombosis, thyroiditis, spontaneous abortion, chronic specific lymph node

inflammation, adverse effect of iron, and septicaemia.

Two conditions which previously have not been observed in association with Y. enterocolitica infection deserve special attention: Acute insulin-dependent diabetes (in two patients) is discussed in Paper V, and development of malignant mesothelioma (in two patients) is discussed in Paper VII. Acute gastrointestinal involvement is further discussed in Paper III, liver involvement in Paper IV, pancreatic involvement in Paper V, and neurological involvement in Paper VI. Other acute manifestation have their counterparts in previous reports (v.s.).

In addition to their acute symptoms, 64 patients had suffered from particular chronic conditions as rheumatic disease, inflammatory bowel disease, hepatitis, thyroid disease, neurologic disease, sarcoidosis or insulin-dependent diabetes for months or even years.

Readmissions and development of chronic disease: Among 160 patients who were readmitted, 75 presented with arthritis, ankylosing spondylitis, or rheumatoid arthritis. 28 patients experienced persistent diarrhoea, and 38 had abdominal pain; chronic colitis was demonstrated in four (Paper III).

Chronic liver disease, in 22 patients, was associated with involvement of other organs, possibly connected with development of malignant disease, and correlated with immunological aberrations, and with an increased mortality (Paper IV).

Chronic disease of exocrine pancreas was diagnosed in four patients, and 11 patients developed diabetes (Paper V), six patients developed chronic neurologic disease (Paper VI), and nine thyroid disease. Nine patients suffered from acute or chronic nephritis, and four from cardiomyopathy. Patients of Bergen University Hospital had a lower mean serum concentration of complement component C4, than had healthy first degree relatives and healthy controls.

At follow-up, 46 patients were dead. Survival and causes of death are discussed in Paper VIII.

In a substantial portion of patients , acute organ involvement developed into chronic disease over years. Therefore, we may conveniently discuss in connection acute and chronic disease of particular organs and compare our observations with recent contributions regarding pathogenesis of acute and chronic disease in yersiniosis.

Particular clinical conditions not discussed in other papers of the thesis:

Arthritis and rheumatism: Among 160 patients who were readmitted, 44 presented with uncomplicated arthritis, and nine suffered from severe sero-negative polyarthritis. When previously diagnosed patients were included, a total of 26 patients suffered from ankylosing spondylitis; at least 14 of them presented the histocompatibility antigen HLA-B 27.
Totally 19 patients suffered from rheumatoid arthritis, and 11 from iridocyclitis.

Development of ankylosing spondylitis subsequently to Y. enterocolitica infection, and especially in HLA-B27 positive patients, is well documented (55, 56); and an association with rheumatoid arthritis has been suggested (57, 58). Our observations confirm previous observations, as nearly 10% of our patients developed severe rheumatic disease. Also minor

joint complaint may be commonly experienced, as 149/337 questionnaire repliers, without rheumatic disease, at follow-up complained of arthralgia or joint swelling.

Our observations support a previous contribution suggesting that the long term prognosis of Yersinia arthritis might be less favourable than previously thought (85). Prolonged persistence of IgA antibodies to Y.enterocolitica has been demonstrated in patients who develop reactive arthritis (86). The antibody response is directed against both chromosomally and plasmid-encoded antigens, indicating that the microorganism may hide within the host for a prolonged time (86, 87, 88,89, 90). However, only bacterial degradation products, not whole bacteria, are present at the site of inflammation in reactive arthritis (91). Reduced levels of erythrocyte C3b receptor may contribute to the pathogenesis of reactive arthritis by affecting the clearance of immune complexes (92).

In a recent study on antibiotic treatment in Yersinia-associated spondyl-arthropathy, disappearance of IgA antibo dies coincided with disappearance of virulent Y. enterocolitica in intestinal biopsies (93).

Thyroid disease: At first admission, two patients presented with acute thyroiditis, in one thyreotoxicosis prompted thyroid resection. Nine patients had thyroid disease diagnosed prior to first admission. During the follow-up period, another nine patients developed thyroid disease; two of them were hospitalized with acute thyroiditis. In the one, with high thyroid antibodies, microscopy of the resected thyroid showed

Hashimoto's thyroiditis (struma lymphomatosa); the other underwent tracheostomy because of laryngeal edema. Two of seven patients who developed chronic thyroid disease also developed chronic liver disease. Among the 20 patients with thyroid disease were 18 females.

Two thyroid disorders have autoimmune aetiology. In Hashimoto's thyroiditis the thyroid acini are progressively destroyed by an autoimmune process, the gland diffusely infiltrated with lymphocytes, and the patient becomes increasingly hypothyroid (94, 95). Graves' disease is caused by the production of thyroid stimulating hormone (TSH) receptor autoantibodies, which stimulate the TSH receptor to increase iodide uptake and cyclic adenosine monophosphate (cAMP) production, inducing production of excess thyroid hormones (96). A high proportion of patients with Hashimoto's thyroiditis and Graves' disease have antibody response to Y. enterocolitica by agglutination or ELISA technique(53, 97, 98). Significantly elevated levels of IgG and IgA antibodies to plasmid encoded release proteins of Y. enterocolitica have been demonstrated in such patients, and antibodies against release proteins raised in rabbits showed specific bands on Western blots with thyroid epithelial cell homogenates (99). Y. enterocolitica antibodies are capable of reacting with the TSH receptor (100). Conversely, Y. enterocolitica membranes have saturable binding sites for TSH (101), and the binding of TSH to the micro-organism is inhibited by IgG from patients with Graves' disease (102). According to a recent report, lymphocytic thyroiditis has been induced in rats by immunizing them with Y. enterocolitica purified membrane protein (103). However, other studies conclude that there is no unique pattern of serological reactivity against Yersinia membranes or the release proteins in patients with autoimmune thyroid disease (104, 105), suggesting that any causal relationship with Grave's disease may be related to T-cell immunity (105).

Acute and chronic nephritis: Four patients were readmitted with acute nephritis, and five developed chronic nephritis. The finding of chronic nephritis supports observation in a previous study, where also deposits of immune complexes and complement C3 were demonstrated in diseased tissue (69).

Chronic heart disease: In four males cardiomyopathy was associated with chronic liver disease; two females presented with acute pericarditis.

Chronic complement aberrations: Twenty-four patients re-examined at
Bergen University Hospital had a significantly lowered mean serum concentration of complement component C4, as compared with first degree relatives and healthy controls without antibody response to Y. enterocolitica. This observation, indicating operation of the classical pathway of complement activation, as well as the finding of generalized urticaria or angioneurotic edema in nine other patients, are in concert with recent reports. Both the alternative pathway and the classical pathway of complement activation are active in killing of Y. enterocolitica. However, plasmid-bearing strains are able to inhibit complement activation and may be protected against its lytic action (20, 106). Complement components may mediate anaphylaxis by histamine release, and may be involved in development of haemolytic anaemia and nephritis. Massive complement activation by microbial products may launch disseminated intravascular coagulation.

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RESULTS AND GENERAL DISCUSSION
(SUMMARY OF THE PAPERS).
PAPER lV.

Saebo A, Lassen J. Acute and chronic liver disease associated with Yersinia enterocolitica infection: a Norwegian 10-year follow-up study of 458 hospitalized patients. J Int Med 1992; 231: 531-535.

At first admission 54/454 patients (11.9 %) with no history of previous liver disease, presented with acute liver involvement evinced by significantly elevated serum levels (two-fold the 97.5% percentile) of bilirubin and/or liver enzymes. Female s seemingly experienced more serious liver involvement than did males: three females only had significant elevation of both bilirubin and two enzymes, and females had the higher frequencies of elevated aspartate transferase (ASAT) levels, and of very high ASAT levels (> five-fold the 97.5% percentile). Females with liver involvement had a higher mean age than females with normal liver function.

Two females and one male presented with substantially higher levels (4 to 5-fold) of ASAT than of alanin e tranferase (ALAT), suggesting severe disease with cellular necrosis and release of the mitochondrial ASAT isoenzyme. These observations were supported by the

demonstration of cellular necrosis in biopsy specimens from 2/12 patients examined; ten had non -specific changes.

Cholecystography or choleangiography was performed in ten patients; in no case was extrahepatic bilary obstruction demonstrated. Testing for hepatitis B antigen in ten patients yielded negative results. Ultrasonography or scintigraphy demonstrated hepatosplenomegaly in four patients examined. Liver involvement was associated with involvement of other organ systems, and significantly correlated with positive tests forantinuclear antibody (ANA). Some patients with liver involvement experienced multiorgan disease.

In the present study, four patients presented with chronic liver disease at the time of Y. enterocolitica diagnosis, in one chronic granulomatous hepatitis with giant cells was demonstrated.

Readmissions: In 22 patients (4.9%) who were readmitted during the follow-up period, chronic liver disease was diagnosed by liver function tests or liver biopsy. In 15 patients, the disease might have persisted since the acute infection. In one patient liver biopsy revealed centrolobular hemorrhagic necrosis, in another unspecific microscopic changes progressed into granulomatous hepatitis over three years. Again, cholecystography or endoscopic retrograde choledochography yielded negative results in five patients examined, and scintigraphy or computerized tomography revealed heptosplenomegaly in four patients. Chronic liver disease was significantly correlated with positive tests for ANA and rheumatoid factor (RF). Several of the 22 patients concomitantly suffered from disease of other organ systems, or multiorgan disease; thus four patients developed cardiomyopathy. A very high mortality of 10/22 (45.5%) was observed in the chronic liver disease group, as compared with 26/426 (6.1%) among patients with no indication of liver disease.

Liver involvement, often with hepatic abscesses, was first time observed in patients with generalized Y. enterocolitica infection or septicaemia.

These patients commonly suffered from debilitating diseases as diabetes or leukemia, or iron overload caused by blood disorders or iron therapy (9, 15, 18, 125). Later slight involvement (5, 39) or even hepatitis (64, 126, 127, 128) have been reported, also in patients without generalized infection.

In the present study, a young man acquired Y. enterocolitica septicaemia after renal transplantation and immunosuppression, but without liver involvement. We have no tangible evidence of liver abscesses among our patients, but suspect this complication in a 73-years-old male who presented with jaundice eleven months after the primary isolation of Y.enterocolitica from faecal samples. His condition had deteriorated for six weeks, and he had lost 8 kg of weight. Liver scintigraphy disclosed numerous cold nodules. Taking into account his severe acute diarrhea the last year, but quite forgetting the positive cultivation of Y.enterocolitica, this finding was without any further ceremony recognized as representing metastases from a supposed colonic carcinoma. The patient died in his home two weeks later.

Most contributions on liver involvement in acute Y. enterocolitica infection have been case reports. However, the frequency of acute liver involvement observed in the present study

may be comparable with frequencies of 5/75 (6.7%) in a previous clinical study (5). According to the size of our material, we have also been able to demonstrate sexn distribution, enzyme relationships, microscopic changes, and radiological and ultrasound findings in acute liver disease; these observations have no counterparts in previous publications.

In 1977, I suggested that a chronic form of liver involvement possibly might be caused by Y. enterocolitica infection (64). In the present study, about one of twenty patients developed chronic liver involvement with serious implications. These observations may constitute a substantial contribution to the understanding of chronic yersiniosis. Granulomatous hepatitis which was seen in two patients support some previous reports (65, 66, 67, 129). This discrete form of chronic inflammation may occur virtually de novo in response to microorganisms which are resistant to destruction by polymorphonuclear leukocytes during the acute inflammatory reaction. Corresponding granulomatous lesions were observed in a lymph node biopsy of a patient with erythema nodosum and acute myocarditis; in three other patients "sarcoidosis" had been diagnosed prior to first admission (Paper II).

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Saeb o A, Lassen J. Acute and chronic pancreatic disease associated with

Yersinia enterocolitica infection: a Norwegian 10-year follow-up study of 458 hospitalized patients. J Int Med 1992; 231: 537-541.

Acute pancreatitis: At first ad mission, eight patients (two males and six females) presented with serum and/or urine amylase levels elevated beyond twice the 97.5 percentile. In all, pancreatic involvement was associated with manifestations as diarrhea, arthritis or liver involvement e tc. Y. enterocolitica serogroup O:9 or O:3 were isolated from faecal samples in case of two patients with antibody titers of 360 viz. 640. Six other patients, in whom cultivation was not attempted, had titers in range 1250-2500.

Chronic pancreatitis. During the follow-up period, none of the patients who had experienced acute pancreatic involvement developed chronic pancreatitis. Four other patients, however, developed chronic disease with moderately elevated amylase levels; in the one associated with chronic colitis. At first admission they had all presented with chronic conditions as insulin-dependent diabetes, rheumatoid arthritis, hepatitis, or glomerulonephritis. In a male patient with haemochromatosis chronic pancreatitis had been demonstrated by ERCP at first admission.

Observations in the present study support previous case reports of pancreatic involvement, or even frank pancreatitis, in association with acute Y. enterocolitica infection (5, 42, 130, 131). In most ca ses Y.enterocolitica infection was diagnosed by antibody response, but at least in one case the microorganism was cultivated from faecal samples (131). A previously

reported patient who developed acute pancreatitis subsequently to ileitis corresponds well with one of our cases (130). In a previous clinical study, Yersinia infection was diagnosed in 21/630 patients with acute abdominal disease, by ELISA technique. Acute pancreatitis was seen in two patients with antibodies to Y. enterocolitica O:3 (132).

In the present study 8/458 patients (1.75%) presented with acute involvement of exocrine pancreas. This should be regarded as a minimum frequency, because most patients were not examined for pancreatic involvement. Nevertheless, it indicates that Y. enterocolitica infection may represent a differential diagnosis in acute pancreatitis.

Chronic pancreatic disease, resembling the conditions presented by four patients at readmission, has previously been observed in association with CD or indeterminate colitis (133). Moreover, decreased pancreatic function has been described in UC (134), whereas acute pancreatitis has been observed in association with CD (135). On this background, the possibility of a non fortutios association of IBD with pancreatitis has been supposed (133, 135). An autoimmunologic basis may be suggested by the demonstration of autoantibodies to the exocrine pancreas in patients with IBD (136). The fact that chronic pancreatitis In our patients was preceded by probable autoimmune conditions may be in accordance with these reports.

Endocrine Pancreas / Diabetes mellitus. Acute insulin-dependent diabetes was diagnosed in a female with concomitant involvement of exocrine pancreas, and in a male with a multiorgan disease not including the exocrine pancreas. He subsequently developed chronic liver disease and cardiomyopathy, from which he died.

Six patients (two males and four females) had suffered from diabetes for several years prior to first admission. Two of the females had insulin-dependent diabetes. One of them suffered from rheumatoid arthritis, and chronic colitis and pancreatitis developed subsequently. In a male patient the disease developed into insulin-dependent diabetes during the follow-up period.

During the follow-up period, another two male and nine female patients developed diabetes; in seven associated with other chronic conditions of possible autoimmune aetiology. Three had insulin-dependent diabetes.

The prevalence of diabetes among patients still alive at termination of the study was compared with the mean prevalence of diabetes in Norway, according to four recent studies (137). A significantly higher than expected prevalence was observed among females aged 30-54 years.

Development of insulin-dependent diabetes requires a genetically pre-disposed individual, and an autoimmune reaction which may possibly be triggered by external factors as viruses or toxins (138, 139). The genes involved are to a great extent located to the major histo-compatibility complex on chromosome 6; their products are involved in immuno surveillance and the recognition of 'self' or 'non-self' (139). The autoimmune reaction may be present several years before the onset of clinical diabetes (139, 140), and is supposed to be

mediated by T-lymphocytes who destroy the islet B-cells (141). Patients with insulin dependent diabetes often suffer from other autoimmune diseases (140).

Two of our patients presented with acute insulin-dependent diabetes in association with the acute Y. enterocolitica infection; in both the disease persisted. Also the unexpectedly high prevalence of diabetes among females 30-55 years old; and the fact that diabetes commonly was linked with other chronic condition s of possible autoimmune aetiology, support the concept that infection with the immunologically competent Y. enterocolitica may initiate diabetes. It is further remarkable that the highest incidence of diabetes in Norwegian children is found in the south eastern part of the country (142) where the majority of the present study population belonged.

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PAPER VI.
Saebo A, Nyland H, Lassen J. Yersinia enterocolitica infection - an unrecognized cause of acute and chronic neurological disease?

A 10-year follow-up study on 458 hospitalized patients.
Med Hypotheses 1993; 41: 282-286.

At first admission, eight patients (five males and three females) with acute infection presented with neurological symptom s. Six had symptoms of CNS, as encephalitis with EEG dysrhythmia in three patients, possible multiple sclerosis (MS) with diplopia and abnormal cerebrospinal fluid (CSF) agarose electrophoresis in one, dizziness and nystagmus etc. in one, and headache associated with peripheral pain and paraesthesias in one patient. Abnormal CSF was seen in two of the patients with encephalitis; in case of an eight-year-old boy with positive tests for RF and cold agglutinins CSF contained 415 mononuclear cells / mm. Two patients had symptoms of PNS as hypaesthesia viz. polyradiculitis. Five patients had antibody titers in range 640-1250, two had titers in range 2500-5000, and one patient with encephalitis had an extremely high titer of 160.000. The patients additionally presented with other acute manifestations as diarrhoea in four patients, arthritis in two, liver involvement in one, and cardiac involvement with atrial fibrillation in one patient. Five of the eight patients with acute neurological symptoms experienced persistent complaints.
During the follow-up period another six patients (two males and four females) developed chronic neurological conditions as possible MS in one patient, EEG dysrhytmia associated with paraesthesias and increased deep reflexes in one, Bell's palsy in one, Meniere's disease in one, trigeminal neuralgia in one, and labyrinthitis in one patient. In five cases, the chronic neurological condition developed with a latency of about seven years.

In 1991, antibody response was evaluated by ELISA in 10/12 patients still alive. Eight of these patients suffered from chronic neurological disease; six of them still had significant antibody

activity, 10-17 years after the diagnosis of yersiniosis. Five of the six patients had persistent IgA activity, indicating chronic antigenic stimulation.

The first reports on nervous system involvement during the acute infection date from the early seventies (5, 51). Three cases of CNS involvement have been reported in association with acute Y. enterocolitica infection, namely two patients with meningitis (51, 143) and one with myelitis (52). PNS involvement with abducens paralysis has been observed in one patient (144), neurogenic amyotrophy in two (52, 145), and Guillain-Barre's syndrome in one patient (5). It has been suggested that Y. enterocolitica may be the responsible agent of some otherwise unexplainable neurological conditions (52).

Immunological and clinical observations in Y. enterocolitica infection may correspond with observations in nervous system disease: in the inflammatory demyelinating disorders the presence of circulating immune complexes (146, 147) and activated terminal complement pathway (148) indicate a carrier state with microorganisms continuo usly present in the host. Moreover, associations between MS and ankylosing spondylitis (149, 150, 151), UC (152) and thyroid disease (153); between Guillain-Barre's syndrome and UC (154); and between peripheral neuropathy and CD (155) have been observed. In the present study, the latency of about seven years for development of neurological disease, and the demonstration of persistent antibody activity in patients with chronic disease, may support the concept of an association with the Y. enterocolitica infection.

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PAPER VII.
Saebo A, Elgjo K, Lassen J. Could development of malignant meso-theliomabe induced by Yersinia enterocolitica infection?
Med Hypotheses 1993; 40: 275-277.

Two out of the 458 patient s developed malignant mesothelioma of pleura viz. pericard; both died after a few months.

Case 1. A 61-year-old woman who presented with a flu-like disease, subsequently developed a right sided pleural exudate, and eventually a growing tumour was observed close to the pleura of the superior lung lobe. She died in respiratory failure.

Case 2. A 34-year-old woman diseased with precardiac pain and weight loss; left sided pleural exudate, venous congestion and thrombosis, and cardiac failure supervened. Thoracotomy revealed a pericardiac tumour with pulmonary metastases; the patient died on the table.

In both cases microscopy of specimen revealed a cellular pattern consistent with malignant mesothelioma, with partly spindle shaped, partly more polygonal epitheloid cells.

Immunohistochemical examination (in case 1.) revealed a strong immunoreactivity for cytokeratins (AE1/AE3), supporting the mesothelial nature of the tumour.

Development of malignant mesothelioma in association with Y.enterocolitica infection has previously not been reported. Malignant mesothelioma of pleura is commonly related to asbestos exposure, and usually encountered among males (156). In heavily exposed populations more than 10 % of subjects may die of mesothelioma (157). The annual incidence of pleural malignant mesothelioma among subjects without asbestos exposure is probably around 1-2 per million (158). Pericardiac mesothelioma is an extremely uncommon neoplasm as its annual incidence is 1 per 4 0 million population (159). Asbestos is recognized as a complete carcinogen or promotor for pleural mesothelioma (160); the mechanism of malignant transformation may involve chromosomal damage (161). Asbestos workers and patients with malignant mesothelio ma may have a high frequency of immune dysfunctions (162, 163), so increased prevalences of positive tests for RF (163, 164) ANA (164) have been observed, and an association with systemic lupus erythematosus has been reported (165). Further has malignant pericardiac mesothelioma been observed presenting as systemic lupus erythematosus (166); and autoimmune haemolytic anaemia has been seen in association with malignant peritoneal mesothelioma (167).

As possible inducers of non-asbestos related pleural malignant mesothelioma have been suggested radiation, minerals, organic chemicals, viruses, chronic inflammation, co-carcinogens, hereditary predisposition, and cigarette smoking (168).

In the present study, a substantial number of patients developed chronic conditions of probable autoimmune aetiology, and positive tests for ANA and RF were correlated with liver involvement with serious implications.

Our two patients with malignant mesothelioma were both females, and had not been exposed to asbestos. Statistically, it would be very unlikely that two out of 458 patients developed malignant mesothelioma. Hence, the association recorded should not be dismissed as implausible, and the possibility that Y. enterocolitica infection might promote malignant mesothelioma should not be disregarded.

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PAPER VIII.
Saebo A, Lassen J. Survival and causes of death among patients with
Yersinia enterocolitica infection. A Norwegian 10-year follow-up study on 458 hospitalized pati ents. Scand J Infect Dis 1992; 24: 613-617.

At termination of the study 46 patients were dead. Two patients, who suffered from multiorgan disease viz. CD, died in association with the acute infection; two others died from malignant mesothelioma after a few months. However, also chronic disorders seemingly promoted by the Y.enterocolitica infection might be supposed to bring a certain mortality.

The observed and expected cumulative survival rates were calculated for 10 years. For males, the observed and expected cumulative survival rates were significantly different after one year of observation (0.9802 < 0.9941; p <0.025), thereafter life expectancy did not deviate from that of the general population. For females, the devi ation of the curves was significant, and still present at the lapse of the 10-year period (0.8980 < 0.9315; p <0.05). Regarding the whole material, the difference between the observed and expected cumulative survival rates remained significant for 8 years (0.9189 < 0.9456; p < 0.025).

The event of death is unusual in acute Y. enterocolitica infection, but has been observed in septicemia, and in fulminant abdominal disease (9, 15, 18, 108). Septicemia generally involves patients debilitated by diseases or medical treatment (9, 15, 16, 17, 18, 108, 169, 170), and carries a very high mortality (171). In the present study, one patient with acute myocarditis, pneumonia and severe liver involvement died two days after admission. Another, with septicemia, was successfully treated with gentamicin (169). In our patient with CD, Y. enterocolitica colitis was one among several factors contributing to death. Death from malignant mesothelioma in association with Y. enterocolitica infection has no counterpart in previous reports.

Among 42 other patients who died during the follow-up period, four died from chronic multiorgan disease, nine from malignant disease, and two from hematological disorders. A very high mortality of 10/22 (45.5%) was observed among patients who had developed chronic liver disease subsequently to the infection. The event of death was also significantly correlated with positive tests for RF, whereas the correlation between death and A NA did not reach significance. Development of RF and ANA constitutes a general feature of diseases at the non-organ-specific end of the autoimmune spectrum. Three of the deceased had positive tests for both ANA and RF.

Multiorgan disease has previously been observed in generalized acute infection (9,15,16). The present study demonstrates that also chronic multiorgan disease, often with fatal outcome, may develop over several years, probably with chronic liver disease as pivot.

The significant differences between observed and expected cumulative survival rates in the present study indicate that the chronic conditions associated with Y.enterocolitica infection may exert a substantial impact on long-time survival.

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CONCLUSION

In the prevalence study, IgG antibody activity to Y. enterocolitica serogroup O:3 was detected in sera from 56 (7.4%) of 755 Norwegian military recruits; indicating that the microorganism may be a much more common cause of infection in No rway than realized to this time. The highest prevalence (21.4%) was found among recruits from Oslo city. Regarding geographical

regions, the prevalence detected among recruits from eastern Norway, including Oslo, was significantly higher than the prevalence detected among recruits from western Norway (11.2% > 5.2%; p = 0.009).

In logistic regression analysis, the following risk factors were found to be independently associated with IgG activity:

1) receiving drinking water from a private we ll (OR) = 3.40, p=0.004), 2) being a resident of Oslo city (OR=2.99, p=0.006), and

3) living in eastern Norway (OR=2.25, p=0.015). The association between unsatisfactory drinking water quality and IgG activity is very important. The interesting geographical impact can so far not be explained.

Seropositive recruits were more likely to report previous surgery for suspected appendicitis than seronegative individuals (OR=4.26, p=0.0024). Among recruits with previous appendectomy, mesenteric lymphadenitis as the sole peroperative finding was more common in patients with IgG activity to Y. enterocolitica O:3 (4/7) than in seronegative patients (1/19)(p=0.01). Particular clinical complaints as recurrent diarrhoea, steatorrhea or joint complaints were not associated with antibody activity.

The clinical study demonstrates that a great diversity of clinical syndromes are associated with the Y. enterocolitica infection.

Most of the acute manifestations observed in the present study have their counterparts in previous reports. Multiorgan disease was observed in several patients. Our observations of malignant mesothelioma development, and of acute diabetes mellitus, represent unique contributions. 160 patient (34.9%) were readmitted during the follow-up period. A substantial number of them suffered from persistent chronic complaints correlated with their first admission symptoms; others developed a diversity of chronic diseases of probably autoimmune character. Chronic liver disease seemingly acted as the pivot of multiorgan disease development, and was associated with immunological aberrations, with a very high mortality, and possibly with the development of malignant disease.

At follow-up, a significantly higher than expected prevalence of diabetes was observed among females aged 30-54 years. In five patients with severe chronic diarrhoea, as in most of those patients who developed chronic neurological disease, significant antibody activity to Y. enterocolitica was demonstrated by ELISA technique after 9-17 years. Especially the IgA activity is important, as this immunoglobulin has a very short half-life.

Its long-time persistence, therefore, indicates chronic infection. The Bergen group of 24 patients had a significantly lowered mean serum concentration of complement component C4, as compared with healthy first degree relatives and unrelated controls.

The observed cumulative survival rates for female patients, and for the whole material, deviated significantly from the expected rates for 10 and 8 years; indicating that chronic

conditions associated with Y.enterocolitica infection may exert a substantial impact on long-time survival.

Although the present investigation by no means prove the existence of a causal relationship between Y. enterocolitica infection and the chronic conditions observed, it is strongly suggestive thereof. Therefore, further studies are required to estimate the role of Y. enterocolitica as an inducer of chronic disease, to elucidate its reservoir and transmission, and to organize preventive and therapeutic measures against this immunologically competent micro organism.

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ADDENDUM

Recently, it has been demonstrated that virulence of Yersinia enterocolitica is closely associated with siderophore production:

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