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FURTHER CLINICAL, EPIDEMIOLOGICAL, AND DIAGNOSTICAL OBSERVATIONS ON PSEUDOTUBERCULOSIS IN MAN

[Following is a translation of an article in the German language by W. Knapp, of the Hygiene-Institut at the University of Tübingen, appearing in the journal Nordisk Veterinaermedicin (Nordic Veterinary Medicine), Vol 16, 1964, pages 18-30. The article is based on a lecture held at the Statens Veterinarmedicinska Anstalt (Government Institute for Veterinary Medicine) at Stockholm, 3 July 1963. Current address of the author: Prof. Dr. med. W. Knapp, Bern, Hygienisch-Bakteriologisches Institut (Institute for Hygiene and Bacteriology), Switzerland.]

Observations during recent years have shown that even in human medicine the pathogenic agent of pseudotuberculosis occurring in various animal species and the symptoms of the disease stimulated by it in man are of increasing importance. Among the pseudotuberculosis cases in man reported in the world literature from 1910 to 1953, only 16 could be identified with certainty as being caused by Pasteurella pseudotuberculosis. This situation has changed after Pasteurella pseudotuberculosis has been shown to be the provocative agent (25) in the special case of mesenterial lymphadenitis in adolescents which, on account of its histological course, had been described by Masshoff (29) as "abscessing reticulocytary lymphadenitis", and this disease has been observed in Europe with increasing frequency.

On account of these observations, this well-known pathogenic agent which had been known for a long time in veterinary medicine was increasingly noticed in human medicine. Evidence for this are the numerous clinical

and laboratory studies. In the course of this lecture, these studies can only be considered as long as they are concerned with clinical or bacteriological problems.

I. Clinical and Epidemiological Observations

1. Forms of the Course of the Disease

Presently two types of the form of the disease are distinguished in clinical studies of pseudotuberculosis in man:

a) the severe, septic-typhous type and
b) the enteral type.

The originally chosen designation "appendicitic form" which had been based on clinical symptomatology has been replaced by the designation "enteral form" because, ordinarily, there are no or only subdued symptoms of an appendix infection. The infectuous changes found especially in the region of the ileocecal lymph glands, the serosa of the ileocecal region of the wall of the distal ileum and the cecum give rise to appendicitis-like discomforts (24, 30).

a). Septic-Typhous Form of the Disease

This very severe form of the disease, which is usually lethal, with toxic symptoms, icterus and coma, and the few cases described in the world literature have been summarized most recently by Knapp (22). A few additional examples show that on account of the non-characteristic symptomatology, the absence of bacteriological-serological studies on a routine scale, and the frequently early use of antibiotics and sulfonamide therapy in case of undiagnosed feverish diseases cover up intestinal infections caused by Pasteurella pseudotuberculosis and an etiological investigation cannot be carried out (6, 23). It is therefore impossible to say anything about the frequency of the septic-typhous form of the disease as long as the routine agglutinate test used in the diagnosis for salmonella, shigella, and brucella has not been extended to the septic-typhous and enteral forms of pseudotuberculosis in man.

b. Enteral Form of the Disease

The clinical appearance of this usually benign form of the disease corresponds to an acute to subacute, rarely chronic appendicitis. However, the corresponding diagnosis is in most cases not confirmed by operative or histological means. The symptoms of gastroenteritis with or without nausea are rarely the chief points of attention.

The first, mostly acute discomforts are observed in the center or lower right part of the abdomen. The temperature lies between 39° and 40° C. The blood exhibits, just as in the case of true appendicitis, a leucocytosis, whereas the sedimentation rate is accelerated -- in contrast with the case of appendicitis (26 and others). At present it is still impossible to distinguish this form of the disease which does not require operative intervention from a a true appendicitis by means of a clinically rapid and certain, differential method of diagnosis. During the operation, a clear, serum-like exudate is found in varying amounts in the abdominal cavity. The mesenteric lymph nodes, especially those in the ileocecal region, are swollen and changed, the mesenterial nodes are frequently diffusely reddish or there is a red tint of the surroundings of the lymph nodes. Finally, there may be a hyperemic swelling of the distal ileum and cecum and an edema of the serosa. The appendix does, in most cases, not exhibit any infection or only minor infectuous changes. Since such affections at the mesenterial lymph glands occur also in the case of virus infections, for instance, in the case of the etiologically ascertained "cat's scratch disease" which has not as yet been ascertained by virus diagnosis, in lymphogranuloma inguinale or tularemia, the etiological characterization, which Lennert (27) has termed "abscessing reticulocytary lymphadenitis" of a morphological substrate, remains a problem for the bacteriologist. Painful, tumor-like enlargements, appearances of an ileus or subileus, or an ileitis terminalis may, in the individual case, be the results of an enlargement of the lymph nodes or an inflammation of the ileum or cecum and may, in rare cases, lead to an ileocecal resection (see reference 24 for literature). An erythema nodosum may be regarded as a sign for a hypergic reaction.

The post-operative convalescence is usually rapid and without complications, even when no antibiotics are administered. Antibiotics should only be used in case of longer or recidividing post-operative abdominal discomfort, continued gastroenteric symptoms, slow or no decrease in

the fever, or decrease in antibody titers lasting several weeks. Tetracycline and streptomycin have been used with success. It is possible to avoid in these cases, by the therapy, the transition from the enteral to the septic-typhous form, a transition which, so far, has not been proven.

According to Masshoff (30), the septic-typhous and the enteral forms of pseudotuberculosis in man are general infections with a cyclic and an infection-dependent course and differ only by degree in kind and extent of the manifestations in the organism. As far as their pathogenetic characteristics are concerned, they are -- according to Masshoff -- more related to typhus abdominalis than to tuberculosis (15, 16, 27).

2. Rapid and Early Diagnosis

The non-existence of a clinically rapid and reliable diagnosis to distinguish the enteral form of the disease which does not require operative action from a true appendicitis led to the demand and search for suitable procedures of an etiological, swift diagnosis at the sickbed.

The proposed antibody test with microscopic slide agglutination (3, 14, 19 Lataix and coworkers) cannot be recommended as a rapid test or probe at the sickbed on account of its uncertain results (spontaneous agglutination, overlapping reactions, et cetera). Moreover, the occurrence of incomplete antibodies has been observed in some cases (20, 28).

The intracutaneous test (35, 36) is also not useful for a rapid or early diagnosis. Mollaret (35, 36) himself states that the test becomes positive usually only 8 days after the operation. Furthermore, it is also true that a positive result of this skin test whose specificity has not as yet been established sufficiently does not indicate anything as far as the activity or inactivity of the process is concerned and whether the reactant patient is sick at the time of the test or whether he has had his Pasteurella infection months or years ago. Moreover, we do not know anything for certain about the time period after the infection, during which the allergic skin reaction can take place. Various observations show also that the skin test may be negative in the case of an acute infection which has been confirmed by detection of the pathogenic agent (1, 32). Mollaret observed positive skin tests for a child with tuberculosis and for persons who had been vaccinated against typhoid, when he used filtrates of

autolysed bacteria cultures. We observed positive skin reactions on guinea pigs which had been sensibilized with Salm. typhosa or Salm. schottmuelleri, respectively, when we tested filtrates of acoustically irradiated cultures of Past. pseudotuberculosis type II and type IV. These observations show that a final judgement of the specificity of the skin tests is only possible when more experimental data from human and animal sources are available. Should the type specificity reported by Mollaret be confirmed, then it would be necessary to carry out up to five skin tests with Past. pseudotuberculosis types I to V in any individual case, if no mixed antigen can be used. However, introduction of the latter presupposes that the skin reaction must be specific with respect to all antigens, that is, also with respect to culture filtrates of Past. pseudotuberculosis types II and IV. In our opinion, this proof has not yet been established for animal or man.

3. Frequency of the Illness

Studies since 1954 here and abroad (literature up to 1958 in reference 22) have shown that when there is planned cooperation between surgeon, pathologist, and microbiologist, Past. pseudotuberculosis infections in man are detected more frequently than could have been assumed so far. Further reports on this subject come from Germany, Belgium, Canada, England, France, Holland, Yugoslavia, Austria, Switzerland, and Czechoslovakia (for literature see reference 24). Frederiksen and coworkers (13) reported on the first cases in Scandinavia. My own published cases up to 1957 (22) have increased to 277 or 267 cases, respectively, at the beginning of 1963. Table I shows a summary of these cases, grouped according to the type of studies made for the diagnosis.

Table I. Observations Made at the Hygiene-Institute, Tubingen (from 1954 to 1963).

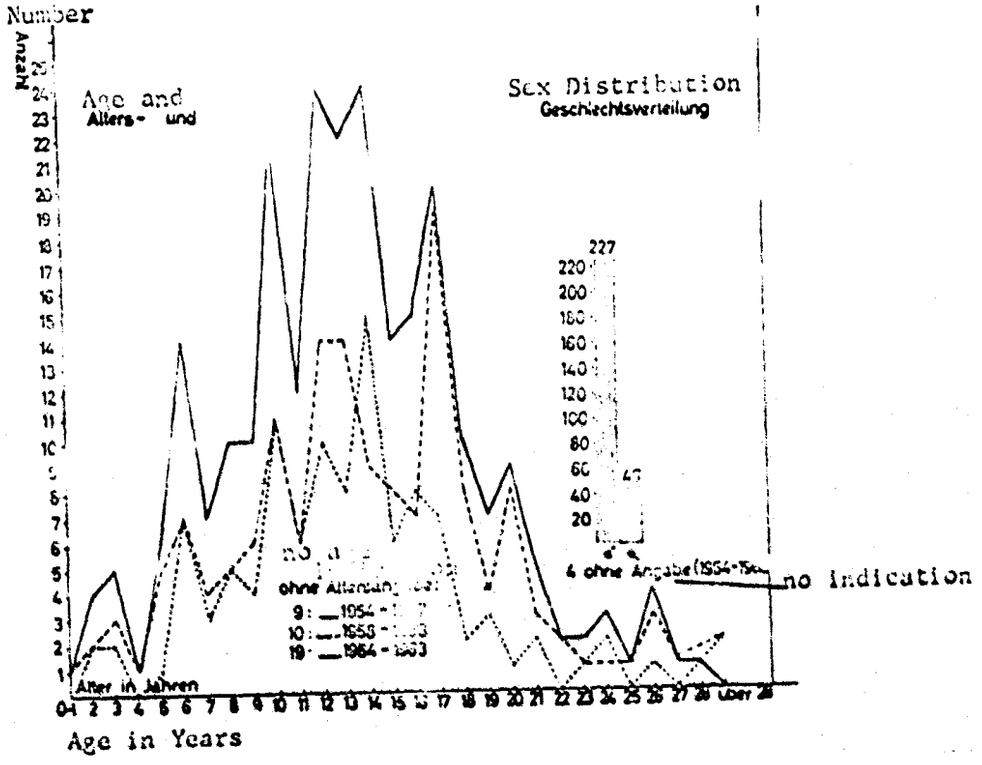
Results	1954-1957	1958-1963	Total Cases
I Detection of pathogenic agent	15	10	25
II Antibody test; characteristic histological findings	81	59	140
III Antibody test; no histological examination (results unknown)	13	84	97
IV Antibody test; histological findings non-characteristic	1	4	5
V No antibody test; histological findings characteristic	7	3	10
Total numbers/excluding V	117/110	160/157	277/267

If one regards the 10 cases given under V in Table I as diagnostically insufficient, a total number of 267 cases remains for which the clinical-operative or histopathological diagnosis of Past. pseudotuberculosis has been bacteriologically established by identification of the pathogenic agent (25 patients), or for which the infection has been made very probable by anti-bodies. Also, in the case of the 10 remaining patients, the surgeon could make a temporary diagnosis for the enteral form of human pseudotuberculosis on the basis of characteristic, clinical, bioptical, and histological findings; the presence of tularemia, cat sickness, or lymphogranuloma inguinale could be excluded by differential diagnosis, but this diagnosis could not be ascertained by serological studies. No antibodies were detected in four of six patients, respectively, or only in very low titers of 1:20 to 1:40 serum dilution were present antibodies against Poast. pseudotuberculosis Type I (22). A repeated examination of blood samples for the control of the titer was impossible for these patients because of external reasons. The question whether these low titers against Past. pseudotuberculosis type I are of diagnostic significance can only be answered when a larger number of observations is available.

The statements made in the literature by various parties are inconclusive.

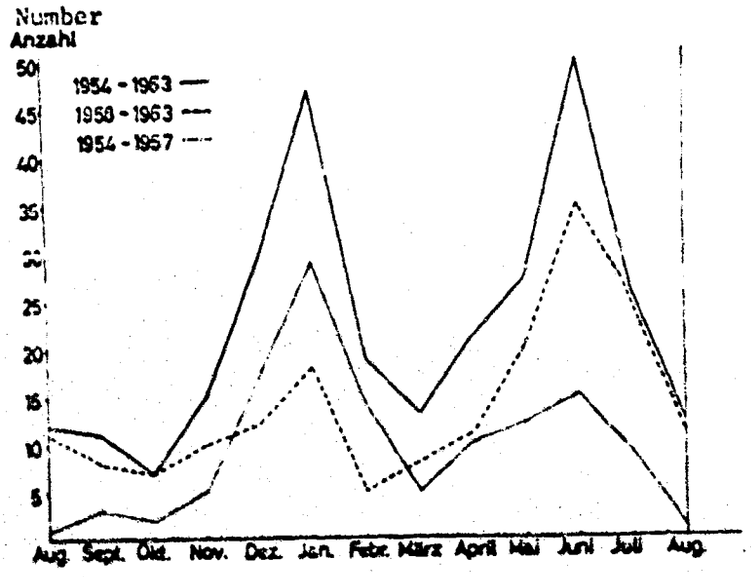
Also, separation of these data according to age and sex (Fig. 1) [captions to figures appended at end] leads to further confirmation of previous communications indicating that, above all, male adolescents are subject to the benign, enteral form of the disease. Our observational data have been obtained from 227 male and 46 female patients. In the case of 4 patients, the sex was not known to us. Of the patients, 204 were from 6 to 18 years of age. The youngest patient was not yet one year of age and the two oldest patients were 35 and 39 years old. There was no indication of the age for 19 patients. Various authors have reported on corresponding observations, especially Mollaret (34) with 30 cases and Daniels (5, 6, 7) with 25 evaluated cases.

Fig. 1. Distribution of Our Own Investigations According to Age and Sex (1954-1963)



Our data exhibit two seasonal maxima of the disease in man. These maxima are in late fall and winter, and spring and early summer, respectively. Hecker (18) reports that of 30 patients, 16 fell sick in the months from November to March, and 4 fell sick in July. Mollaret observed a similar seasonal distribution for 30 cases described as pseudotuberculosis; however, not all of these cases are serologically sufficiently confirmed as infections with Past. pseudotuberculosis type II or IV, respectively. On the other hand, Haenselt (17) observed the evaluation of 33 cases, histologically diagnosed as abscessing reticulocytary lymphadenitis; of 28 serologically tested patients, 26 had antibodies against Past. pseudotuberculosis -- a distinct accumulation of the disease, especially in the spring months from April to June.

Fig. 2. Seasonal Distribution of Our Own Investigations (1954-1963)



So far, it has not been possible to find a satisfactory explanation for the seasonal variation in the frequency of the disease in man. Perhaps some information will

be gained from veterinary studies of the seasonal frequency of the disease in animals which are directly or indirectly in frequent contact with man (for instance, cats, guinea pigs, rabbits, dogs, hamsters, et cetera). The observation of Borg and Thal (2) that of 2,500 rabbits studied, 6.2% died of pseudotuberculosis and of these, the largest portion during the months from November to March, is of epidemiological significance.

The available publications and our own observations do not yield any certain answer to the epidemiologically important question whether among patients from rural areas, that is, patients with regular or repeated direct or indirect animal contact, exists a higher frequency or pseudotuberculosis or not. Statements by various authors concerning this question are not based on exact studies of a sufficiently large number of examinations. The possibility of contact infection is discussed in various reports on the disease of single animals, brothers and sisters, communities, and groups in the environment of sick anumals or animals who had been sick some days or weeks before, or dead animals (cats, hamsters, guinea pigs, birds, and pet dogs), some of which had antibodies against Past. pseudotuberculosis. However, a certain proof is missing in all cases (see literature in 24). Only Daniels succeeded so far in establishing a simultaneous proof of the presence of Past. pseudotuberculosis type IA in the discharge from the bowels of a patient and the latter's canary bird. Daniels considered the cause for the disease in his patient to be in the discharge from the bowels by the canary bird. The antibodies of the patient increased up to 1:5,200. This first-time isolation of Past. pseudotuberculosis has, meanwhile, also been accomplished by Kampelmacher in 1963 and represents, in addition to the pathological findings, another indication for the enterogenous production of pseudotuberculosis in man (5, 11, 12, and others).

4. Immuno-Biological Observations

Nothing is known about the immunology in man after infection with Past. pseudotuberculosis or after active immunization with killed pathogenic agents. This is in contrast to various animal observations. Our plague-hygienic knowledge about pseudotuberculosis in man has not led to any corresponding studies. The present increase in the number of child and adolescent patients justifies considering whether an attempt should not be made to combat pseudotuberculosis in man by active immunization of animals kept in close contact with children, above all, dogs, cats, birds,

hamsters, rabbits, and guinea pigs. The observations carried out by Thal (37, 38, 39) with the avirulent strain No 32^{IV} of Past. pseudotuberculosis might possibly become of practical significance.

The first studies of Thal (37) with Past. pseudotuberculosis strain No 32^{IV} provided proof that intraperitoneal injection of the living, avirulent strain leads to an anti-infectuous immunity against Past. pseudotuberculosis strains of the heterologous type, which lasts approximately five months and that the serological heterogeneity of the types of Past. pseudotuberculosis are opposed by an immunobiological uniformity. Thal (37, 38) observed type III only during immunization with toxic, that is, exotoxin-forming strains of Past. pseudotuberculosis.

Starting with the additional observation that virulent Past. pseudotuberculosis strains behave in some respect like pathogenic intestinal germs and may lead to mesenterial lymphadenitis in man, Thal studied (39) the further problem whether, subsequent to oral administration, strain 32^{IV} reaches the intestine and is stored in the mesenterial lymph glands and whether its persistence in the intestinal lymph nodes leads to solid immunity.

Thal was able to show that after peroral infection of guinea pigs, a persistence of the germs of approximately three weeks (longest observation period) in the lymph glands (small intestine, cecum and rectum) and a strong immunity against a virulent Past. pseudotuberculosis strain type I existed. Isolation of the germs from blood, lungs, spleen, and liver was impossible, even on enriching nutrients.

However, the same immunization success did not occur in the case of two other perorally administered strains of type IV (190^{IV}, $Ikegaki^{IV}$) so that the type-specific, smooth-O-antigen IV, and the rough-O-antigen which is common to all types cannot alone bring about the inoculative protection. The immuno-chemical studies of Davies (8, 9 and others) should perhaps be drawn upon for the immunological interpretation of this observation. Thus, it was possible to detect strain 32^{IV}, against expectations, as determinant final group in O-antigen tyvelose. Avirulent strains and rough forms of Past. pseudotuberculosis and salmonellas are supposedly not capable of synthesizing 3,6-di-desoxy sugar corresponding to the virulent smooth form. Details cannot be discussed here.

Our present knowledge on clinical, data, pathogenesis, epidemiology, prophylexis, and a rapid, certain, clinical diagnosis of human infections with Past. pseudotuberculosis is as yet quite incomplete. It is true that

We consider the enteral course of the infection as the true one, without knowing the infection chain, however, we know nothing for certain about the incubation period, the moment of generalization and manifestation of the agent in the organism, the kind of immunity after the disease has passed, and the frequency of occurrence. This knowledge must remain incomplete as long as no observational results of epidemiologically exactly known group diseases or epidemias are available and as long as serological diagnosis of distinct fever-like abdominal and intestinal illness with or without typhoidal character has not been carried out on a routine basis with strains of Past. pseudotuberculosis types I-V, and as long as no greater attention is given to the isolation of Past. pseudotuberculosis from blood and discharge from the bowels.

An elucidation of this as yet open question cannot be brought about by the surgeon, the pathologist, and the microbiologist without assistance from the veterinarian. Their cooperation must be intensified -- especially for the clarification of the epidemiology.

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English Summary Appearing at End of the Original Article

Further Clinical, Epidemiological and Diagnostical Observations on Pseudotuberculosis in Man.

A survey is given of the importance of infections with Past. pseudotuberculosis; ~~and~~ their higher frequency during the last years is stressed.

The well-known types of the disease, the typhoid and the enteritic form are described, and

Based upon the author's material, collected during one decennium, the immunologic and epidemiologic aspects are discussed.

The elucidation of the epidemiology of this infection is only possible by an intensive cooperation between human and veterinary medicine.

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