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AN INVESTIGATION OF THE INCIDENCE OF
PASTEURELLA PSEUDOTUBERCULOSIS IN THE POPULATION

[Following is a translation of an article by Dr. Joachim Schmidt, of the Institute of Medical Microbiology and Epidemiology of the University of Leipzig, in the German-language periodical Zentralblatt für Bakteriologie, Parasitenkunde, Infektionskrankheiten, und Hygiene (Central Journal of Bacteriology, Parasitology, Infectious Diseases and Hygiene), Vol 180, No 4, 1960, pages 530-536.]

While in veterinary medicine the pathological picture of pseudotuberculosis has been known since the end of the last century and has come under observation in the most varied species of animals, especially rodents, human infections have been observed only rarely.

In searching through the literature up to 1953 Knapp found only 16 cases that could be regarded as adequately established bacteriologically as *Pasteurella pseudotuberculosis* illnesses. Almost without exception they ran a course typical of severe septicemic and typhous general infections, and usually with fatal outcome.

Alongside these severe clinical pictures Knapp and Masshoff in 1954 set a mild form, which appeared clinically with appendicitis-like, more rarely gastroenteritic symptoms. They were able to demonstrate that the special form of inflammation of the mesenteric lymphatic glands described on the basis of extended histological studies by Masshoff and Dölle in 1953, the so-called suppurative reticulocytic lymphadenitis, is in fact a disease caused by *Past. pseudotuberculosis*. By 1957 Knapp had found 117 bacteriologically or (and) serologically established cases, and thus has at his disposal the largest amount of observational material. Besides that, *Past. pseudotuberculosis* illnesses of the mild form have also been described by other investigators, such as Graber and Knapp (1955), Kuhlmann and Herrmann (1955), Prodhragyai and Fodor (1956, cited according to Knapp), Berg and Hecker (1956), Brandis (1957, cited according to Knapp), Christiansen (1957), Haenselt (1957), König and Maurath (1957), Hecker (1957), Ingelrains and Foupard (1957, cited according to Knapp), Braun

and Müller (1957), Flamm (1958, cited according to Knapp), Holch (1958, cited according to Knapp), J. Schmidt (1959), Lindemann (1960), and also H. Schmidt (1955) and Becker (1954) (in the case of the last two articles without bacteriological or serological evidence). The cases observed by us consisted of eight serologically established illnesses (and one doubtful Pasteurella illness), the agent having in one case been obtained from a mesenteric lymphatic gland (J. Schmidt).

Since the detection of the causal agent involves difficulties, the detection of specific agglutinating antibodies by means of the Widal test plays all the greater part in establishing a diagnosis. It must be taken into account, however, that the species *Past. pseudotuberculosis* can be subdivided on the basis of different O antigens into five serological types (Types I to V). For that reason tests must be done with all five antigens, although infections with Type I predominate by far. In appraising the results attention must also be given to the fact that there are some antigens in common between *Past. pseudotuberculosis* Type II and *Salmonella* bacteria of group B (O antigens 4 and 27), as well as between *Past. pseudotbc.* Type IV and bacteria of the *Salmonella* group D (O antigens 9 and 46) and of the *Salmonella* group H (O antigen 14).

Positive agglutination titres with the antigens of serological Types II and IV can thus be evaluated only after corresponding absorption experiments are carried out, while reactions with antigens of serological Types I, II, and V are to be regarded as specific for *Past. pseudotbc.* infections.

In the majority of the articles cited, agglutination titres of 1:80 and higher in the patients are spoken of; Knapp found, as we did, values up to 1:12800, most often between 1:160 and 1:640. Very high titres, or titres in the range mentioned with a rise and later decline in repeated examinations of the serum, when taken in conjunction with the clinical picture leave no doubt as to the diagnosis of a *Past. pseudotuberculosis* infection. There is more difficulty in appraising lower titres such as 1:20 and 1:40, found by Herrmann even in healthy persons, while Knapp was unable to find any *Pasteurella* agglutinins among 1601 serum samples sent in because of suspicion of lues or *Salmonella* infections or in 76 clinically and operatively proved cases of appendicitis. Among the 20 cases established histologically by Hecker, blood samples were available from 10 patients for serological examination, and while 7 of these turned out positive, they showed surprisingly low titres, between 1:20 and 1:80. Knapp comes to the conclusion that the question of the diagnostic significance of such low titres cannot be answered until larger sets of tests are available.

Our Own Investigations

In connection with the appraisal of *Pasteurella* agglutination titres we were interested in the question of the possible

occurrence of specific antibodies against *Past. pseudotuberculosis* in healthy persons and in persons with other diseases.

Material and Methods

For this reason we examined a total of 509 blood samples [see Note]. Of these, 256 were from healthy males and females from 16 to 75 years of age, the majority belonging to age groups from 20 to 60 years. Most of these were blood donors. Besides these, 253 sera came under study that had been sent to our institute for the performance of other reactions in connection with suspicion of other diseases (typhus, paratyphus, enteritis, dysentery, Bang's disease, listeriosis, leptospirosis, toxoplasmosis) or made available to us by the University Children's Clinic.

[Note] For making these blood samples available I thank Dr. Haase, doctor in charge of the blood bank; Dr. Hempel, of the University Children's Clinic; and Dr. Kohler, Leipzig.

The investigations extended over a period of a year all told. As evidence of the specific antibodies we made use of the Widal agglutination test, using living antigens of the 5 serological types of *Past. pseudotuberculosis*. The strains were incubated for 48 hours on agar slants at 22° C, washed off with physiological salt solution, and set to Widal's density (500 million germs per cm³). The sera were tested in geometric series from 1:20 to 1:160. After 20 hours in the water bath, readings were taken, and if necessary the series was extended. As controls we used sera obtained by immunization of rabbits with extracted *Past. pseudotuberculosis* antigens of serological Types I to V. Negative antigen controls were set up with physiological NaCl solution. The absorption tests we carried out according to the usual rules of bacteriological technique.

Results

As the total result of our examinations we might say in advance that we were only able to find very occasional positive *Pasteurella* agglutinations.

Among the healthy persons were found in two blood samples titres of 1:20+ with Type I antigen, and in another serum the titre was 1:40(+). With this serum we carried out absorption tests. After absorption with the homologous antigen (Type I) no more antibodies were detectable, but after absorption with a heterologous antigen (Type 5) antibodies against Type I (1:20+) could still be observed. Specific antibodies against Type III were always lacking, while antibodies against Type V were found in one case with a titre of 1:80 (+). Here again proof of specificity could be obtained through absorption tests. In another serum we found a titre of 1:160+ with Type V antigen. Checking back yielded the information that there had been no clinical indications of illness. A second blood sample taken 8 weeks later still showed a titre of 1:40+, which on the basis of absorption tests is to be regarded as specific. With antigens of

Types II and IV agglutinations up to a titre of 1:160+ could be obtained somewhat more often, but after absorption with Salm. paratyphi B or Salm. typhi no more antibodies could be detected in any of these cases, so that these were cases of non-specific paragglutinations and not of specific Pasteurella reactions.

Among the sick persons, too, whose blood samples were sent to us for the purpose of making other tests, and also among the sick children only scattered positive findings were obtained, which are divided as follows among the Past. pseudotuberculosis types: in 2 sera with antigen Type I a titre of 1:20+, in one serum with antigen Type V a titre of 1:80+, in one serum with antigen Type V a titre of 1:40+. Absorption tests carried out in the last two cases provided proof of the presence of specific Pasteurella antibodies. As in the group of healthy persons, we were unable to find any antibodies against Type III here, while agglutinations against the antigens of Types II and IV (in some cases with titres up to 1:320) could be recognized as non-specific paragglutinations on the basis of absorption tests.

It is interesting that in one serum the titre with antigen V reached the high figure of 1:6400(+). Checking back revealed that this was the case of a 58-year-old patient who exhibited a gastroenteritic clinical picture. Under symptomatic treatment the ailment died away after 8 to 10 days. A second blood sample taken 16 days later still showed a titre of 1:400(+). In both sera the Widal agglutination test with the other Pasteurella antigens as well as with the usual Salmonella, Shigella, and Brucella antigens was negative. This was thus an illness caused by Past. pseudotuberculosis of serological Type V which could be serologically established. This case has already been described in detail in our article on human Past. pseudotbc. infections (J. Schmidt).

In another serum sent in for the purpose of other Widal reactions Pasteurella agglutinins were found against Type I with a titre of 1:160(+) and against Type V with a titre of 1:320(+). Blood samples requested on the basis of this finding yielded the following result: 10 days later with antigen Type I a titre of 1:40+, with antigen Type V a titre of 1:160(+); another 4 weeks later, with antigens I to V negative. Clinically [see Note] the 15-year-old patient showed a severe illness, diagnosed as meningoencephalitis, with incipient disturbances of the consciousness and states of confusion, although no symptoms of neurological deficiencies existed. The phenomena gradually disappeared under symptomatic therapy and administration of penicillin and streptomycin, and complete recovery occurred. Serological tests for the presence of antibodies against typhus, paratyphus, enteritis, dysentery, brucellosis, spotted fever, listeriosis, toxoplasmosis, and poliomyelitis came out negative with repeated examinations; the Pasteurella titres mentioned

represented the only positive finding. Blood cultures were not undertaken. Thus there could be no sure etiological explanation of the clinical picture. Very probably, however, this was one of the rare septicemic-typhous disease patterns caused by *Past. pseudotuberculosis*.

[Note] For making the clinical data available I thank Prof. Dr. Rechenberger, then deputy director of the University Medical Clinic, Leipzig.

Discussion of the Results

The serological studies carried out by us on 509 serum samples (256 from healthy and 253 from ill persons) had the result that only very scattered positive *Pasteurella* agglutination titres were found. A total of 6 sera reacted with the antigen of Type I and 5 sera with the antigen of Type V, while antibodies against the antigens of serological Types II, III, and IV could not be found. After deduction of the two serum samples from the aforementioned cases of illness, there remain 9 positive agglutination tests that can be discussed from the point of view of a latent infection. The question then arises of the specificity of these low titres. We attempted to clarify this matter by absorption with homologous and heterologous antigens and found that insofar as the sera could be subjected to absorption we had been dealing with *Pasteurella* agglutinins that must have been formed in the course of dumb immunization or abortive disease. The low titres found are therefore to be adjudged specific. Another point in favor of specificity (according to Knapp), though an indirect one, is the absence of *Pasteurella* antibodies in the overwhelming majority of the blood samples examined both from healthy persons and from persons with unrelated diseases. The incidence of inapparent infections with *Past. pseudotuberculosis* among the population may therefore be characterized as extremely low.

No studies of the length of time that antibodies remain in circulation could be made with the positive sera. We know, however, from more accurately followed cases of human diseases that while high antibody titres do relatively quickly drop to low values, these may nevertheless remain observable for months. We could also cite similar findings in immunized animals, where titres of 1:20 and 1:40 could still be found after several months (J. Schmidt, unpublished).

We were unable to give any explanation for the fact that among the few positive agglutination tests found there were some of the otherwise very rare reactions with the antigen of the serological Type V. In order to rule out non-specific paragglutinations that are as yet unknown, we ran absorption tests with various species of bacteria (*Salmonella* bacteria of the serological groups A, B, C, D, E, *dyspepsia coli* bacteria of the group O55, *Listeria* of Types I and IV), but without being able to show antigen relationships. No studies are available concerning a

possible higher incidence of Type V strains among animals in the area we are able to draw upon.

The accidental discovery of a sure case of a Pasteurella pseudotuberculosis illness caused by Type V but with a clinical picture of gastroenteritis must be regarded as an interesting by-product of these studies, which were concerned with determining the incidence of infection in the population. The other case of illness with a septicemic-typhous course, clinically diagnosed as meningoencephalitis, does not seem to us adequately established etiologically, though the high titres (double infection?) justify assuming a Past. pseudotuberculosis infection with great probability. The only other possible explanation would be that of an anamnestic reaction, but no studies are available of the course of such a reaction with positive Pasteurella titres in man.

Studies done by us from this point of view (J. Schmidt, unpubl.) on the rabbit showed that even animals immunized with Past. pseudotuberculosis Type I showed no fluctuations in titre in the sense of an anamnestic reaction when given injections of heterologous antigens (Past. pseudotuberculosis Type III, Salm. newport antigen), or in the case of a few animals, very slight ones.

Summary [see translator's note]

Agglutination tests of 509 blood samples from healthy persons and from patients suffering from other illnesses for the presence of Past. pseudotuberculosis antibodies led in only nine cases to finding low titres, the specificity of which in the majority of cases could be established by absorption tests. The incidence of such infection can accordingly be characterized as very low. As an interesting side result, one sure case of Past. pseudotuberculosis illness was found, caused by Type V, and also one probable Past. pseudotuberculosis infection which clinically ran a septicemic-typhous course.

[Translator's note] The summary is printed in German, English, French, Spanish, and Russian. The other four appear to be translations of the German summary, and the English translation is less well done than the rest. This is an independent translation of the German summary.

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