Pasteurella pseudotuberculosis Information as Background for Understanding Plague

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NEW information on pseudotuberculosis would further understanding of plague and improve our ability to cope with it, for the causative agent of pseudotuberculosis and the plague bacillus are closely related. Persons in the best positions to obtain the data needed are those whose primary duties lie outside the field of plague research—physicians, laboratory diagnosticians, sanitarians, epidemiologists, veterinarians, and members of fish and wildlife services. The required information can be obtained in the absence of plague cases. Its collection would simply require a small effort in addition to standard procedures.

Human pseudotuberculosis was thought to be a rare and highly fatal acute septicemic disease until about 10 years ago. Then, however, it was recognized that the disease occurs in an enteric form as a mesenteric adenitis causing symptoms of appendicitis. Since that time, numerous cases have been reported throughout Europe, 200 in France alone and a greater number in Germany (*1–3*). In Europe, pseudotuberculosis appears to be widespread among many species of mammals and birds, but plague is absent. In North America, we have wild animal plague foci, and there is evidence that pseudotuberculosis of mammals and birds may be much more widespread than plague (*4*). If this is true, why do we have no reported pseudotuberculosis infections in man? Since 1937, when the first case in the United States was reported by Topping (*5*), only a handful of scattered cases in human beings have been recognized. Either pseudotuberculosis is not a common disease in this country, or we are a decade behind the Europeans in recognizing its presence. Recent studies in Canada (*6*) have led to the conclusion that "human infection with *Pasteurella pseudotuberculosis* is not unusual in the Edmonton region and is responsible for at least some cases of mesenteric lymphadenitis." Dr. K. F. Meyer (*7*) has urged a search for pseudotuberculosis because of its importance as a separate disease entity. Such a search is also essential to progress in understanding plague. Support for this view derives from five categories of information: the immunological relationship, the antigenic similarity, the pesticin-fibrinolysin-coagulase activities of *Pasteurella pestis*, the dissociation of *P. pestis* in the direction of *P. pseudotuberculosis*, and the reversible alteration of *P. pseudotuberculosis* characters in the direction of *P. pestis*.

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Immunological Relationship

Early plague investigators knew that vaccination of animals with *P. pseudotuberculosis* could protect them against plague, and numerous attempts have been subsequently made to explain this finding (*8*). Although little or no support has been presented for a reverse relationship, there is reason to believe that under certain conditions one should be able to demonstrate protection against *P. pseudotuberculosis* by vaccination with *P. pestis*.

Antigenic Similarity

Although cross protection against disease by one or more common antigens indicates that *P. pseudotuberculosis* and *P. pestis* have something in common, additional strong evidence that they are closely related comes from demonstrating that they share numerous common antigens regardless of the antigens' immunological value. For example, of 18 antigens which we were able to distinguish from each other by gel-precipitin methods, 13 are found in both *P. pestis* and *P. pseudotuberculosis* (*9, 10*) :

P. pestis

F T D B C E G H I J K L O Q V W N M

P. pseudotuberculosis

This antigenic analysis is by no means comprehensive, and if it were extended until 50 or 100 antigens could be distinguished, most of them would probably be common to both species.

Pesticin-Fibrinolysin-Coagulase

After we found recently that plague strains which show fibrinolytic activity also produce pesticin, and vice versa, we learned that Russian workers had been reporting complete correlation between fibrinolytic and coagulase activities. In plague bacilli, it appears therefore that pesticin, fibrinolysin, and coagulase are genetically linked, whereas *P. pseudotuberculosis* lacks all three of these activities (*11*). This finding raises the important question as to whether these three genetically linked bacterial properties, present in *P. pestis* and absent in *P. pseudotuberculosis*, are responsible for certain differences between the two diseases. If this question turns out to be productive for future research, then finding an answer to it is fundamental to understanding not only plague and pseudotuberculosis but also certain other infectious diseases.

[Since this paper was presented, preliminary research on this question suggests that the three bacterial properties do influence the characteristics of the disease caused by *P. pestis* (*12*).]

Dissociation of P. pestis

P. pestis can give off variants or "mutants" which lack the pesticin-fibrinolysin-coagulase properties and resemble *P. pseudotuberculosis* with respect to these properties. A number of other characters which differentiate these two species have been observed to change in the direction of *P. pseudotuberculosis* (see chart). When changes in the direction of *P. pseudotuberculosis* occur one at a time, the bacterium is still easily identifiable as *P. pestis*. The more of these changes which occur, however, in a variant of the plague bacillus, the more difficult it becomes to distinguish the bacillus from *P. pseudotuberculosis*. Russian investigators have been convinced (*13*) for many years that, after phage action or prolonged storage, plague cultures will yield variants indistinguishable from *P. pseudotuberculosis*.

Dissociation of *P. pestis* in the direction of *P. pseudotuberculosis*

PHENOTYPIC CHARACTER	P. PESTIS		P. PSEUDOTUBERCULOSIS
glucose-6-phosphate dehydrogenase	—		+
phosphofructokinase	+		—
glycerol	—	⟶	+
rhamnose	—	⟶	+
melibiose	—	⟶	+
toxin	+	⟶	—
capsular antigen	+	⟶	—
motility at 20° C	—		+
urease	—	⟶	+
fibrinolysin	+		
coagulase	+	⟶	—
pesticin I	+		

NOTE: Arrows indicate changes, which have been observed in various laboratories, in the identifying characters.
SOURCE: Summarized from the discussion by Brubaker and associates (*11*).

Alteration in Direction of P. pestis

Mating of *Escherichia coli* with *P. pestis* and with *P. pseudotuberculosis* has been demonstrated to the extent that the fertility factor, F, can be passed from *E. coli* to these pasteurellae (*14*). In this work a fertility factor which carries a gene for fermenting lactose (F-lac) was used for easy identification of clones which harbor the F. One of the unexpected findings by Dr. W. D. Lawton of our laboratory was that some of the *P. pseudotuberculosis* exhibited a number of *P. pestis* characters while harboring the F-lac episome but returned to normal when the F-lac was lost. These F-lac cultures temporarily resembled *P. pestis* in giving negative reactions for glycerol, rhamnose, urease, pesticin sensitivity, and in glucose-6-phosphate dehydrogenase tests. The cultures were also reversibly nonpigmented on hemin agar, were VW^-, able to grow on oxalate agar, and were avirulent for mice.

Discussion

In speaking of *P. pseudotuberculosis* and *P. pestis*, Burrows and Bacon (*10*) said: "The similarities of the two species have led many to hypothesize that the former may, in some way, be concerned in the endemicity of plague. The sporadic derivation of *P. pestis* from *P. pseudotuberculosis*, an organism having wide geographical and host range, would nicely explain the otherwise puzzling alteration of plague epidemic and quiescence throughout history." Whether or not one agrees with this hypothesis, undoubtedly current bacteriological research is providing more and more evidence to support the idea that *P. pestis* and *P. pseudotuberculosis* are so intimately related that a real understanding of one will have to include an understanding of the other. Widespread occurrence of *P. pseudotuberculosis* in mammals and birds and indications noted in our laboratory by Werner A. Janssen, microbiologist, that this microorganism may possibly cause lethal infection in fish would seem to single out *P. pseudotuberculosis* as one of the most versatile of bacterial pathogens. The extent of incidence of human pseudotuberculosis in North America certainly is unknown at present; such information is needed as background for understanding the problem of plague.

Recommendations

Collection of information on pseudotuberculosis would be greatly facilitated if a cooperative effort could be established between physician, laboratory diagnostician, sanitarian, epidemiologist, veterinarian, and personnel of fish and wildlife services. Useful procedures which might be added without difficulty to current routines include:

1. Urease and motility tests in gram-negative bacterial isolations
2. A test for *P. pseudotuberculosis* antibodies in examination of serums for antibodies against salmonellae and in cases of atypical appendicitis.
3. Bacteriological culture of lymph nodes in cases of mesenteric lymphadenitis
4. Forwarding of suspect cultures or serums promptly to interested laboratories
5. Determination of plague and pseudotuberculosis patients' blood group
6. Statistical analysis of hospital records for indications of pseudotuberculosis.

Notation of the blood group of plague and pseudotuberculosis patients will supply information for future evaluation of the suggestion of Pettenkofer and Bickerich (*15*) that plague patients of group O have a very unfavorable prognosis. This suggestion is based on the possibility that such patients, who cannot produce antibody against their own antigen H, also cannot produce antibody against a plague antigen similar to the H antigen.

As an example of the possible usefulness of hospital records, a recent die-off of grackles in Maryland might be considered. Investigation of the grackles' disease apparently received impetus when "one woman stated that six of her swine had died of an unidentified disease about a week after she noticed many sick and dead blackbirds in the vicinity of the hog feeder" (*4*). In Knapp's experience (*2*) the benign form of human pseudotuberculosis occurs predominantly in adolescent males. Would hospital records show an increased incidence of appendicitis in adolescent males in the area following the die-off of grackles?

Summary

Information on the occurrence of *Pasteurella pseudotuberculosis* in man and animals of North America is needed as background for under-

standing the problem of plague. *P. pseudotuberculosis*, which can cause human infections with symptoms of appendicitis, is so closely related to the plague bacillus that a real understanding of one disease will have to include an understanding of the other. Support for this view is derived from information on the immunological relationship between *P. pseudotuberculosis* and *Pasteurella pestis*, their antigenic similarity, the pesticin-fibrinolysin-coagulase activities of *P. pestis*, the dissociation of *P. pestis* in the direction of *P. pseudotuberculosis*, and the reversible alteration of *P. pseudotuberculosis* characters in the direction of *P. pestis*. A small effort added to standard procedures by persons not concerned primarily with research could yield the needed information.

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New Pesticides Laboratory

The Public Health Service has established a Pesticides Research Laboratory on the south campus of the University of Miami School of Medicine, Richmond, Fla.

The first phase of construction has been completed. The unit, now ready for occupancy, provides facilities for chemists who will work on technical problems with Office of Pesticides staff members. A second unit will be opened next spring to provide for more fundamental research, including investigation of possible long-term effects of pesticides on human health. The total scientific staff of the laboratory will be about 40.

The site was chosen because of its proximity to researchers studying effects of pesticides, as used in Dade County, Fla., on human health and pesticide investigators in the university's pharmacology department.