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LINGERING FORMS OF PLAGUE IN LABORATORY ANIMALS
Report IV*

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LINGERING FORMS OF PLAGUE IN LABORATORY ANIMALS

Report IV*

Generalization of Lingering Forms of Plague Following the Lowering
of the Resistance of the Macroorganism

Following is the translation of an article by L. B. Adimov, published in the Russian-language periodical Shornik Nauchnykh Rabot Elistinskoy Protivochumnoy Stantsii (Collection of Scientific Works of the Elistinskaya Antiplague Station), Issue I, 1959, pages 93--107. Translation performed by Sp/7 Charles T. Ostertag Jr.

* Report I Trudy of the Rostov-on-Don State Scientific Research Antiplague Institute, vol XV, issue 1, 1959.

Reports II and III - Ibid, vol XVI, 1959.

Chronic plague of rodents was the subject of consideration by many investigators (Simond, 1898; Kolle and Martini, 1902; Gotschlich, 1903; Hata, 1904; Zabolotnyy, D. K., 1906; Shchastnyy, S. M., 1910, 1912; English Commission for the Investigation of Plague in India, 1906--1912; Suvorov, S. V., 1926; Williams, 1926; and many others). However, opinions on its epizootological importance have differed since the time of the first works, which based the participation of rodents on the implantation of plague in nature.

Thus Simond and Gotschlich, and Kolle and Martini, assume that chronic plague of rats can condition the preservation of this infection during interepizootic periods and provide the beginning for a new acute epizootic. The English Commission, on the basis of a great many personal observations supplemented with the histological investigations of Ledingham (1907), arrived at the conclusion that chronic plague does not have any significance for implanting this infection in nature and represents a stage of the successful recovery from an acute form of the disease. Therefore, the Commission felt it more correct to name the chronic form of plague as resolving plague, thus stressing the impossibility of its subsequent aggravation. The works of the English commission exerted a great influence on many investigators and for the course of several dozen years the predominant point of view was that the generalization of lingering forms of plague was impossible. This assumption was shaken by the works of Dujardin-Beaumont (1912), Churilina, A. A. (1915), Gayskiy, N. A. (1926, 1944), Wu Lien-Teh (1928), and Grikurov, V. S., (1934) in respect to the role of hibernating rodents in the transfer of plague causative agents from one epizootic season to another. As regards non-hibernating rodents, then just as recent as 1944 V. N. Fedrov, in analyzing the voluminous factual materials on the epidemiology of plague which had accumulated for half a century, wrote that there were no bases

to consider chronic plague of non-hibernating rodents as a means of perpetuating this infection in nature.

However, in recent years undeniable facts have been obtained on the generalization of lingering forms of plague both in hibernating and non-hibernating rodents, and many authors express the opinion that the lingering forms play a role in sustaining a plague enzootic (Petrulina, O. M., 1950; Tumanskiy, V. M., Sokolova, N. M. and Fedutina, N. K., 1951; Pletneva, N. A., 1957; Malafeyeva, L. S., 1957; Anisimova, T. I., 1959, and others). They propose that the reason for the aggravation of lingering forms of plague may be the lowering of the protective powers of the organism when the rodents fall into unfavorable conditions of existence. Nevertheless, in the literature we did not find one work which gives direct proof that unfavorable influences on the organism of a rodent which has a lingering form of plague led to a generalization of the infectious process.

In connection with this, we made an attempt to clear up experimentally to what degree unfavorable factors may influence the course and outcome of lingering forms of plague. In the literature there are indications that such attempts did not lead to positive results (Akhundov, M. G., 1940; Fedorov, V. N., 1944).

For lowering the resistance of the organism we used cortisone, and also starvation. The selection of methods was not accidental. It is known that cortisone in large doses is a powerful factor, lowering the resistance of animals to various infectious diseases. It has been established that the administration of cortisone to white mice sharply increases their sensitivity to the plague causative agent (Payne, F. E., Larson, Walker, Foster and Meyer, 1955; Shirayayev, D. T. Lalazarov, G. A., Vorona, I. M., Melashchenko, L. K., 1958). It must be noted that such an effect was not observed in immunized mice (Payne, Larson, Walker, Foster and Meyer, 1955). Hayashida, 1957, reports of the significant lowering in the resistance to the plague microbe of white rats which had received adrenocorticotrophic hormone. Along with this, there are observations testifying that poor fatness with insufficient nourishment increases the sensitivity of animals to plague (Klets, E. I., Khrustselevskiy, V. P., Kolesnik, R. S., Kudinova, Z. S., Olkova, N. V., Smirnova, L. A., 1957).

Experimental Data

For clearing up the possibility of a generalization of lingering forms of plague following the influence on the macroorganism of unfavorable conditions, we conducted tests on white rats and white mice. In the tests we used adult white rats weighing 180--250 g and white mice weighing 18--25 g. We used cortisone from the French firm Roussel. Infection of the animals was accomplished by the subcutaneous introduction into the area of the left haunch of a 0.5 ml microbial suspension, prepared in a physiological solution from a 24-hour agar culture of the plague causative agent, incubated at 28°. The dead and the destroyed animals were subjected to a pathoanatomical and bacteriological investigation. The latter was carried out by means of seedings on agar plates with material from the site of

infection, the regional lymph nodes, liver, spleen, lungs and blood. The microscopic study of the pathological anatomy of the test animals was conducted in the pathohistological laboratory of the Z. D. Khakhina Institute. The results of these investigations are used in the present report.

The activity of the cortisone was checked in preliminary tests.

The activity of the preparation for white mice was determined by means of infecting them with the P. pestis 1 vaccine strain following the preliminary, for 4 hours prior to infection, single intramuscular administration of various doses of cortisone to the animals. Following the infection of mice with a dose of 200 million microbial bodies of P. pestis 1, some of the "cortisoned" animals died from generalized plague, while all the mice which did not receive the preparation survived. Stemming from this test, for the provocation of lingering forms of plague in white mice we favored 8 mg as the best dose of cortisone, since higher doses proved to be toxic.

In the literature we were not able to find any works which shed light on the influence of cortisone on the plague infectious process in white rats. In connection with this we tested the activity of cortisone during the infection of white rats with the virulent P. pestis 773 strain. The cortisone was introduced one time into the muscles of the right haunch four hours prior to infection. Observations of the animals were conducted for a month. The results of the test are presented in table 1.

The death of the animals from plague set in on the 6th and 7th day following infection. The growth of the plague microbe on agar plates in seedings from the organs and blood of the dead animals was abundant in the majority of cases.

As can be seen from table 1, the administration of cortisone considerably increased the infectious sensitivity of white rats to plague.

Stemming from this test, we accepted a dose of 50 mg as optimal for the provocation of lingering forms of plague in white rats.

Being persuaded that cortisone lowers the resistance of white mice and white rats to the plague causative agent, and having determined the optimum doses of the preparation, we switched to carrying out the main tests.

We infected 24 white mice with 1, 10, 100 and 1000 microbial bodies of P. pestis 773. For each dose 6 animals were taken. Table 2 presents the results of the test on the 29th day after infection.

All the surviving mice appeared fully healthy, ate well, and were lively. On the 29th day following infection 8 white mice, which had survived from 10 and 100 microbial bodies, received 8 mg each of cortisone intramuscularly in the right haunch. The remaining 6 animals did not receive cortisone, assuming that animals with lingering forms of plague could be found only among those which survived from large infecting doses (see Report I).

From those which had received the injection of cortisone, 4 white mice died and the remainder were destroyed on the 9th and 10th days following introduction of the preparation. All the white mice, with the exception of one, No 1631, were less than noteworthy. Three of them died of causes which had no relation to plague infection. No lingering forms of plague were found among the animals which were infected with one microbial body and destroyed on the 38th day following infection.

White mouse No 1631, which had survived following infection with 100 microbial bodies of *P. pestis* 773 and which had received 8 mg of cortisone on the 29th day, died on the 37th day following infection. Upon autopsy the following pathologoanatomical changes were detected in it: The subcutaneous tissue was sharply hyperemic, especially in the inguinal and axillary areas, sharply edematous on the left side and moderately edematous on the right. The edema of the subcutaneous tissue reaches its greatest expressiveness in the left inguinal area and at the site of infection. At the site of infection necrosis of a cream-green color is detected in the haunch muscles, in the central part of the necrosis the muscles are fused, along the periphery -- diffusely saturated with a purulent exudate; the adjacent subcutaneous tissue is edematous and hemorrhagic, and increased in volume. The left inguinal and left iliac lymph nodes are sharply enlarged. The right inguinal lymph node is moderately enlarged. The liver has a clayey color. The spleen is enlarged significantly and has a dark perise color. In the bacteriological investigation the profuse growth of a typical culture of the plague microbe was noted in seedings from the organs and blood.

In the histological investigation of white mouse No 1631 a focus of complete necrosis of the muscles and the purulent inflammation of the surrounding tissues was noted, and plague bacilli were encountered among the cells of the exudate; the muscle fibers, separated into layers with exudate, were necrotic. In the regional lymph nodes hyperplasia of the reticular cells and diffuse plasmocytosis are observed. In the spleen, plethora of the pulp and impoverishment by cellular elements are noted most sharply, the follicles are large and bordered with a narrow zone of necrosis in which small accumulations of the plague bacilli are encountered. The liver is plethoric, the cells of the parenchyma have sharp dystrophic changes. In many of the intralobular capillaries there are accumulations of plague bacilli, penetrating into the surrounding tissue. Plethora is noted in the lungs and there are minute foci of acute inflammation. In the capillaries of the septa and between the cells there is a large number of plague bacilli.

The data cited testifies that in white mouse No 1631, which died on the 37th day following infection, a generalized plague infectious process was established with the presence of agonal septicemia.

Two tests were conducted with the aim of provoking lingering forms of plague in white rats. In the first test, 41 white rats which had survived following infection with various doses of *P. pestis* 773 received a single dose of 50 mg each of cortisone intramuscularly. For 19 animals 49 days passed from the time of infection to the moment the cortisone was administered, and for 22 animals -- 38 days. The 30 control white rats were infected with 1000 microbial bodies of *P. pestis* 773, and of these, 20 animals received 50 mg each of cortisone intramuscularly four hours prior to infection.

All the test animals remained alive and were destroyed after 17--20 days following the administration of cortisone. Ten of these had lingering forms of plague, which were characterized by the presence in the tissues of encapsulated abscesses, filled with necrotic contents. In seedings from the contents of the abscesses the growth of the plague microbe was abundant. In two white rats, in which the abscesses were localized at the site of infection, the regional inguinal lymph nodes were considerably enlarged and in seedings on agar plates the growth of the plague causative agent was observed in the form of single colonies.

During histological investigation no changes were found in the rats which would make it possible to suspect an aggravation of lingering forms of plague.

The facts of the isolation of the plague microbe from the lymph nodes, regional to the site of disposition of the encapsulated abscesses, produce a foundation to consider that encapsulation is a relative barrier for the plague microbes and the latter may penetrate from the foci of affection beyond their limits.

Thus in this test the provocation with cortisone did not lead to an aggravation of lingering forms of plague.

In the control test the cortisone considerably lowered the resistance of white rats to plague: By the 15th day following infection, out of the 20 animals which received the preparation 17 succumbed from generalized plague, while out of the 10 which did not receive the preparation only 4 died.

In the second test, 37 white rats, which had survived following infection with various doses of *P. pestis* 773, were subjected to the influence of unfavorable factors. These rats received subcutaneously 50 mg each of cortisone twice with an interval of 13 days between injections. From the time of infection up to the moment of the first administration of the preparation, 31 days passed for 17 of the animals, 34 days for 18 animals, and 109 days for 2 animals. Five days prior to the first injection of cortisone all the white rats were transferred to a limited nutritive diet, on which they were kept up until the end of the experiment. Up until this day the ration for the rats included milk, dark bread and oats. The milk and bread were withdrawn from the ration and the amount of oats was cut in half. In place of milk the rats drank water. Observations of the animals lasted for 23--28 days following the first injection of cortisone. Over this period of time 7 white rats died and the remainder were destroyed in

specific periods. In the majority of animals, both those that died and those that were destroyed, a significant emaciation was noted.

Of the rats which died, 5 did not have any pathologoanatomical changes which were suspicious for plague and cultures of plague microbe were not obtained from them. The remaining two rats which died, No 859 and No 867, merit special attention.

While rat No 859 was infected with 100 microbial bodies of *P. pestis* 773. It received a single dose of cortisone on the 34th day following infection. It died on the 9th day following administration of the cortisone, that is on the 43rd day following infection. Upon pathologoanatomical investigation the following were detected: the rat was of average fatness, the subcutaneous tissue was sharply hyperemic. Disposed in the left inguinal area was an encapsulated abscess with the dimensions of 0.7 x 0.5 x 0.4 cm, filled with a dense necrotic content of a creamy color. The surrounding tissues and the capsule of the abscess were hemorrhagic. In the liver, sectors of an intense red color alternated with sectors of a clayey shade. The spleen was small. The lungs had changed sharply. The left lung and the middle lobe of the right were enlarged in volume, dense (consistency of the liver), in a profile had a red color, and did not collapse. In the middle lobe of the right lung there were several small grayish-white necrotic nodes. The upper and lower lobes of the right lung had a bright red color, were moderately edematous, and pneumatic.

During bacteriological investigation the typical culture of the plague microbe grew in the seedings from all the organs and blood. The growth of the causative agent was especially profuse in seedings from the contents of the abscess and the lungs, and somewhat less profuse in the seedings from blood.

Pathohistological investigation yielded the following results: The left inguinal lymph node was completely necrotic, in the dead tissue there were many plague bacilli, along the periphery the necrosis was surrounded by a zone of purulent inflammation. The capsule only partially circumscribed the focus of affection, and there where it was not the purulent infiltrate penetrated far into the surrounding cellular tissue (see photos 1 and 2). The spleen was plethoric. In the liver there was granular degeneration of the cells of the parenchyma, many Kupffer cells were increased in size, and in some degeneration of the nuclei was observed. In the left lung and in the middle lobe of the right there was a diffuse acute inflammatory process. In the exudate there were erythrocytes, leucocytes and serous fluid with a mass of plague bacilli (see photo 3). In the other sections of the lungs on a background of sharp plethora there were numerous small pneumonic foci with a serous and a serous-leukocytic exudate, in which there were many plague bacilli. There was sharp granular degeneration in the kidneys. The adrenal glands were plethoric.

The data cited testifies that in white rat No 859 a generalization of

a lingering form of plague took place. The plague causative agent was distributed beyond the limits of the localized focus of affection in the regional lymph node and caused an extensive acute pneumonia. Death of the animal set in with the symptoms of a quite intensive bacteremia.

The virulence of a subculture, obtained from the blood of white rat No 859, was tested in the next days following its isolation by means of infecting white rats, guinea pigs and white mice, and it turned out to be preserved at a high initial level for all three species of animals.

White rat No 867, infected with 1000 microbial bodies of *P. pestis* 773, received cortisone twice, in 34 and 47 days following infection. It died on the 52nd day following infection. Upon autopsy, emaciation of the animal was noted, there was a well expressed hyperemia of the subcutaneous tissue, a large encapsulated abscess at the site of infection, a moderate enlargement of the regional lymph nodes, atrophy of the spleen, and plethora of the lungs. In seedings from the contents of the abscess the growth of the culture of plague bacteria was profuse, and in the seeding from the regional inguinal lymph node individual colonies of the plague causative agent grew.

Histological investigation of white rat No 867 did not expose any signs which would testify to a generalization of the infectious process. For a certain expanse the capsule of the abscess had an insignificant thickness.

Thus, even a lethal outcome did not cause a generalization of plague in white rat No 867: The plague microbes remained localized within the limits of the primary complex.

Upon investigation of the surviving animals, lingering forms of plague were detected in four white rats. In two rats the encapsulated abscesses were found at the site of infection, in one in the retroperitoneal lymph node, and in the last one, No 953, at the site of infection and in the liver. Seedings of the contents of the abscesses in all cases yielded profuse growth of typical colonies of the plague microbe.

There is interest in white rat No 953, which was destroyed on the 50th day following infection. Upon autopsy no other changes were found besides the thin walled encapsulated abscess at the site of infection and the large encapsulated abscess in the liver. However, during bacteriological investigation cultures of the plague microbe grew not only in seedings from the contents of the abscesses, but also in seedings from the spleen, lungs (moderate growth), and blood (single colonies).

The histological study of white rat No 953 did not expose any changes in the organs which would verify a generalization of a lingering form of plague.

Discussion

In our previous investigations it was established that the plague causative agent may be preserved for a long time in the organism of white rats, guinea pigs and white mice with lingering forms of plague in these animals (Report I). In this the virulence of the causative agent remained at a high initial level for all these three species of animals, regardless of the species of the host in which the plague microbe coexisted for a long time (Report II). In white rats which had endured infection with a 50% lethal dose of plague bacteria, a determination was made of the intensity of immunity after 25--71 days following infection (Report III). The white rats, among which some of the animals had lingering forms of plague, showed a relative resistance to repeated infection both by small (10 Dcl) and by large (200 Dcl) doses of plague microbes. As a rule, in the rats which died following repeated infection, weakly expressed pathologoanatomical changes took place and a complete absence of plague microbes was observed or there was a very small saturation of the rats by the causative agent. However in a small segment of the rats, following repeated infection there emerged a general secondary specific affection of the lungs. It was noteworthy that only in these animals did premortal bacteremia develop and the saturation of the blood with plague microbes was high. The facts of the death of rats with the symptoms of extensive plague pneumonia testify that the various organs of animals which had endured subcutaneous infection with plague may acquire a different resistance to the repeated introduction of plague bacteria. These data agree with the results obtained by other authors. Thus it is known that in plague the lungs are immunized poorly and with retardation in comparison with other organs (Batzaroff, 1899; Zhukov-Verezhnikov, N., 1940; Pokrovskaya, M. P. and Kaganova, L. S., 1947). Jawetz and Meyer (1944), following infection of immunized white mice and guinea pigs with not very great doses of virulent plague bacteria, observed in the animals, which died in remote periods, extensive plague bronchopneumonia in the absence of affection of other organs. These authors view such a phenomenon as a result of incomplete or partial immunity. They also propose that the toxin, liberated upon the death of the plague bacteria in partially immune organisms, lessens the resistance of the lung tissue to the introduction of the causative agent in it and furthers the onset of the above described pneumonia, whereas the liver and spleen remain unaffected in view of their resistance to toxin and cellular activity.

According to the data of Shirayev, D. T. (1957), in house mice which have survived following an initial infection with a 50% lethal dose of a virulent strain of the plague microbe, a non-susceptibility to repeated infection develops. However, "the degree of immunity in house mice which have recovered from plague is not high, and following the repeated infection with 10--25 multiple doses of plague microbes a considerable number of mice die from plague."

Thus it is apparent that in some cases between the causative agent and the organism of the host there may be an accumulation of that type of interrelationship during which the plague microbe preserves its high virulence, but the organism possesses a relative or incomplete immunity.

The protective role of the tissue barrier in the form of the abscess capsule is very relative. In the absence of sufficient immunity such a barrier is quite surmountable for the plague microbe. Thus, in the tests by O. N. Trubchaninova and L. N. Makarovskaya (1958) following the previous completion of treatment of plague infected guinea pigs with insufficiently effective doses of streptomycin, the germination of the capsule of the abscesses formed with plague bacteria took place and the development of an acute generalized infection. The above cited cases of the isolation of cultures of the plague microbe from the lymph nodes, regional to the site of finding the encapsulated abscesses, also confirms the possibility of the penetration of the causative agent from the abscesses into the surrounding tissues. Finally, the degree of expression of the capsule of the abscesses is various, sometimes over a certain expanse it is so thin that it is detected only by histological investigation.

Thus there are bases to assume that prerequisites exist, under which lingering forms of plague may produce a generalized infectious process. It is fully possible that the reason for aggravation in such cases is the lowering of the infectious resistance of the macroorganism.

The results of the experiments conducted support this assumption. The lowering of the resistance of the organism of animals led to the aggravation of lingering forms of plague in several of them and had a lethal outcome with the symptoms of generalization and premortal bacteremia.

The lowering of resistance of white mice far from always led to the aggravation of lingering forms of plague in them. Out of 15 mice, in the organism of which the plague causative agent was preserved, generalization with a lethal outcome set in only in one. Aggravation emerged in a white rat from the group of animals which was on a starvation diet and had been subjected to the influence of cortisone. The lowering of protective forces in the animals of this group was so significant that some of the white rats died from extraneous causes. Nevertheless, in one of the dead rats, No 867, the plague microbes remained within the limits of the primary complex.

In the white mouse the generalization was characterized by a more or less equal involvement of the various organs and tissues in the infectious process, while in the white rat an extensive affection of the lungs predominated with an insignificant involvement of the other organs in the process.

Conclusions

1. In our setup of tests cortisone lowered the natural resistance of white rats and white mice to plague.

2. The lowering of the infectious resistance in these species of animals may lead to a generalization of lingering forms of plague and to a lethal outcome with a high saturation of the blood with the causative agent.

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Table 1

Influence of cortisone on the flow of plague in white rats, infected with *P. pestis* 773

No. of group of animals	Number of animals in group	Infecting dose (in microbial bodies)	Dose of cortisone (in mg)	Died		Survived
				from generalized plague	with negative result of bact. inves.	
1	4	1000	25	1	1	2
2	4	1000	50	2	-	2
3	4	1000	100	3	-	1
4	4	----	50	-	1	3
5	4	----	100	-	2	2
6	4	1000	---	-	-	4

Table 2

Results of infection of white mice with various doses of *P. pestis* 773

No. of group of animals	Number of animals in group	Infecting dose (in microbial bodies)	Died from plague	Duration of live of the animals which died (in days)	Survived
1	6	1	0	-	6
2	6	10	1	9	5
3	6	100	3	5, 5, 15	3
4	6	1000	6	5, 5, 6, 8, 8, 23	0

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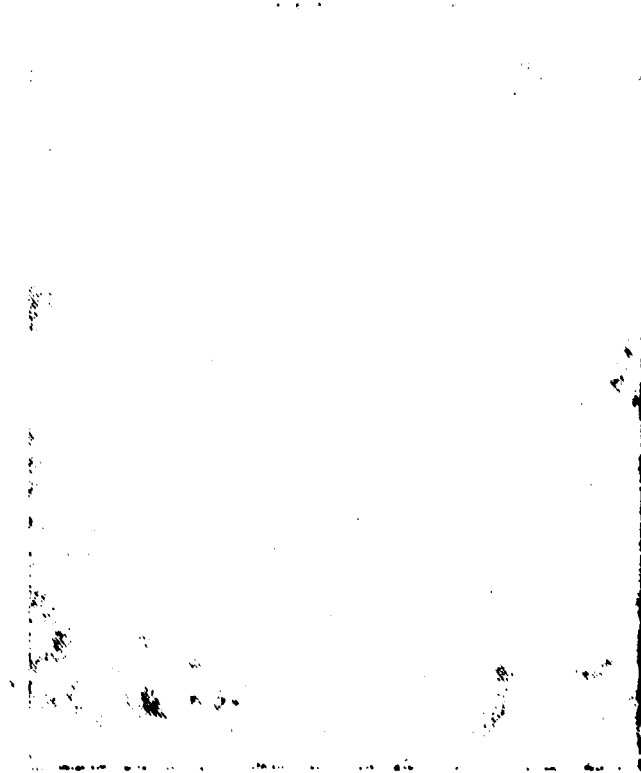
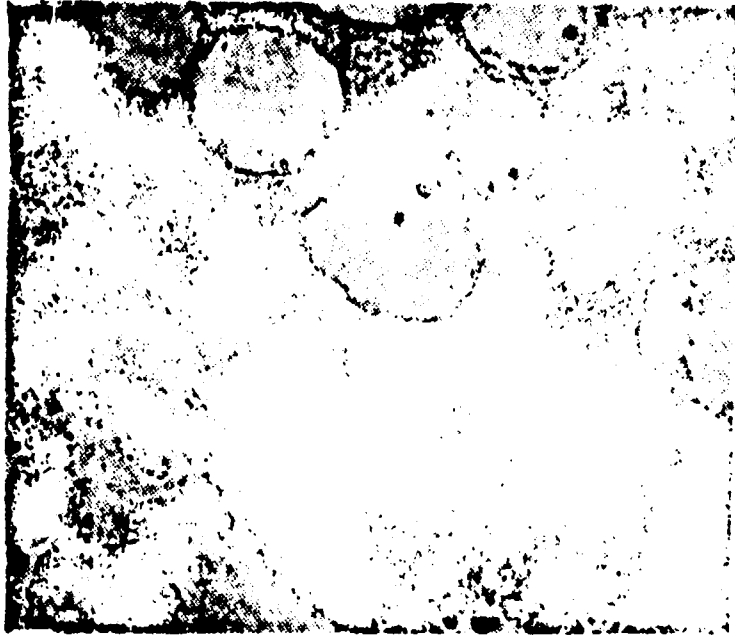


Photo 1. White rat No 859. Microscopic section of the wall of the abscess. In the center the capsule is seen, and below -- the purulent infiltrate.

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Photo 2. White rat No 859. Microscopic section of the wall of the abscess: The capsule is absent, the purulent infiltrate is penetrating unimpeded into the subcutaneous fatty tissue.

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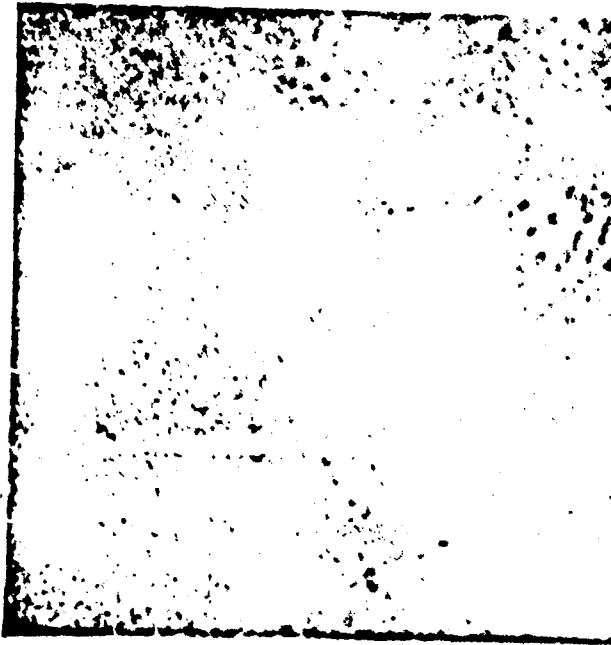


Photo 3. White rat No 859. Smear -- imprint of the lung. There is a mass of plague bacilli in the exudate.