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DEPARTMENT OF THE ARMY
Fort Detrick
Frederick, Maryland

INTEREPIZOOTIC CONSERVATION OF PLAGUE IN ITS INVETERATE FOCI
WORKING HYPOTHESES

[Following is a translation of a paper by M. Baltazard, Y. Karimi, M. Eftekhari, M. Chamsa and H. H. Mollaret, of the Institut Pasteur de Teheran (Pasteur Institute of Teheran), reprinted from Bulletin de la Société de Pathologie Exotique (Bulletin of the Society of Exotic Pathology), Vol 56, No 6, November-December 1963, pages 1230-1241.]

What is there still standing of the thesis which we have been defending for the past ten years, which makes the presence of rodents resistant to the plague the key to the long life of infection in inveterate foci?

On the one hand, we believe that we have ourselves established proof, in nature as well as in the laboratory, that resistant rodents are incapable of conserving the infection in their organisms: the high percentage of "chronic" forms among animals surviving at the end of an epizootic outbreak being merely a phenomenon without lasting effect, and "delayed relapses" or "belated generalizations," if they do exist, not being susceptible of implication as a "habitual mode" of survival. Sources of low-grade pathogenicity found in nature at the end of an epizootic outbreak, which multiply "chronic" forms among rodents, can not insure future infection either. Even the more modest role which we had assigned to these resistant rodents (1), as mere "nourishers" of fleas that conserve the plague can no longer be defended: in nature, as in the laboratory, the fleas of these rodents show neither longevity nor a cycle which would permit them to insure perpetuation of infection.

Moreover, it is now evident that this resistance is but the consequence of the existence of the plague. If this consequence were not ineluctable, and if it were proved that there exist authentic inveterate foci where no resistance to infection may be demonstrated among any population of any species of rodent, we would have to recognize that this is merely an epizzotic phenomenon, and not the necessary condition

of which our research in nature seemed to us to have furnished proof in Kurdistan. We could, in fact, no longer deny, as we have been doing for a long time, that burrowing Sciuridae have the possibility of insuring by themselves, in certain burrows, a long life for infection. These Sciuridae are, in fact, typically sedentary, great burrowers, with deep, permanent burrows which are always occupied or reoccupied, like the spermophile Citellus fulvus which we studied in Iran, those "ground squirrels" (Citellus) and "prairie dogs" (Cynomys) so well observed in the U.S.A., those "sousliks" (Citellus), and, above all, those "souroks" (Marmota) whose habits researchers in the USSR have studied for so long, and have shown that they clear out and reoccupy burrows emptied by the plague. Now, if we believe that it is in the life of the deep chambers of the burrows of these species, in inveterate foci, that alone is to be sought the persistence of the plague bacillus, it does not seem that in the many works accumulated in the past any precise research has demonstrated a resistance characteristic of those species.

Certainly, as early as 1910 McCoy (17), who must, in our view, be considered as having initiated the idea of resistance and of its epizoological importance, drew attention to the fact that Citellus captured in plague foci resisted experimental innoculation better than those captured in regions where wild plague did not exist. K. F. Meyer (18), in 1942, confirmed McCoy's observations on Citellus beecheyi, but his work was difficult to interpret because of the differences in susceptibility which he observed between males, females and young. We ourselves, in systematic experimentation by innoculation of cultures of ground up infected organs, or by flea bite, which we carried out on Citellus fulvus captured in the heart of the focus of Kurdistan, have been able to observe their extreme susceptibility to infection. It is true that these Citellus came from two populations which we have kept under observation since 1950 (2), and in which we have never observed the existence of infection.

On the other hand, Tinker and Alechina in the USSR apparently demonstrated in 1955 the difference in susceptibility between two populations of the small souslik Citellus pygmaeus. This work, which appeared in an untraceable publication (22), is known to us only by the critique made of it by Lévi and his collaborators (15), who reproach those authors for the "non-simultaneity of their experiments and certain other errors." This is, no doubt, why Lévi on his part, resumed, along with Valkov, Minkov and Novikova, the series of experiments on Citellus pygmaeus captured in the same region where he had just demonstrated a difference in susceptibility between various populations of Meriones meridianus. The results of Lévi and his collaborators are known to us only through a short résumé presented at the Tenth Conference on parasitological problems and diseases of natural focality, in October 1959 (14). The authors write: "In simultaneous experiments there was studied the susceptibility to plague of various populations

of small sousliks on territories with an epizoological past and with differing ecological characteristics. These experiments have shown that small sousliks captured in the past [Note: this expression "in the past" cannot be translated any more clearly: does it refer to Citellus kept in captivity for a long time? (translator's note)] in the endemic region near the village of Zavetnoe [Note: north of Elista, on the right bank of the Volga (translator's note)] were ten times more resistant than the sousliks captured in the sovkhoz of Tchernozemelsk [Note: south of Elista, on the right bank of the Volga (translator's note)] and on the left bank of the Volga (Dosang)"[Note: we again thank our bibliographer, Mme. M. Chirzadi, for her translations, which her profound knowledge of the subject makes particularly valuable].

These results suggest that this resistance to infection may doubtless also be found in other places where the interaction of the species concerned and the natural conditions will have given the sousliks (and even the marmots, on which there is still research to be done) the function of the conservation of the plague in their burrows. And we think we can state that where proof will be found that this resistance does not exist among these species, the reason is that other rodents must be responsible for the conservation of the infection, as is doubtless the case in this zone of Dosang studied by Lévi and his collaborators, where the small souslik is susceptible, but where Meriones meridianus shows a high level of resistance. It is, moreover, certainly not to be ruled out that several species may take part on the same spot in conserving the infection under the condition -- a necessary one, in our view -- that they dig or frequent or reoccupy the deep burrows which are the reservoirs of infection. This is indisputably the case in Kurdistan with the field mouse Microtus irani and the small hamster Cricetulus migratorius, which are perpetual usurpers of the burrows of meriones, as soon as the latter are no longer there to defend them. It cannot be ruled out that this might also be the case with a number of other species, and to restrict ourselves only to Microtus and Cricetulus, for example Microtus brandti, whose possible resistance in the USSR has been known since the researches of Lekreneva (6), Smirnova and Vassyukhina (21) and Chtchekounova (7), and whose infection has just been found in nature by Kovaleva (12) in marmot territory in Bayan-Khongor in western Mongolia; with Microtus gregalis, whose infection, already known in Tian-Chan, has been confirmed by Lavrentiev and Polouliakh (13), to be precise among Microtus established in the sweepings of marmot burrows; with Cricetulus barabensis, known for its resistance to the plague in Transbaïkalie since the work of Von Jettmar (8) (9), the research on which by Soviet authors, commented on by Rall (20) have shown natural infection in Manchuria; finally, in the United States, with Microtus californicus, the resistance of which has been known since the work of McCoy (16), who experimented on animals captured in nature in the environs of San Francisco and showed at the same time the extreme susceptibility of Citellus beecheyi captured at the same place; this Microtus has recently been found infected in the same

region by Kartman and his collaborators (11), who have also demonstrated differences of receptivity in this rodent between neighboring populations.

The resistance to infection of certain populations of rodents in inveterate foci does appear, therefore, to be considered as an ineluctable consequence of the presence of the plague. But can this consequence be at the same time the necessary condition of which we continue, on the evidence of our observations in nature, to say that it is the key to long life of infection? Prolonged observation over a period of fifteen years in the field has shown us the rapid disappearance of "dead" burrows, of whatever kind, a disappearance which is more rapid than the repopulation of the territory by rodents. The entrances of the "dead" burrows on the meriones M. vinogradovi and M. tristrami and of the other species burrowing in cultivated land disappear in a few weeks, or, at the most, a few months, under the action of plowing, the passing or grazing of cattle (particularly sheep and goats), or merely of wind and weather. The entrances of the permanent burrows of M. persicus on hillsides or in heaps of stones, and those of M. libycus in salty, uncultivated land are not subjected to the same causes of rapid destruction; nevertheless, the wind and its cargoes of dust and storms generally cause them to disappear from one summer to the next when these burrows are no longer inhabited. Therefore, the only ones remaining open after an epizootic outbreak are the inhabited burrows: those of rodents (or those reoccupied by rodents) which have survived extermination by plague, that is to say, those of the rodents (or those reoccupied by the rodents) which are resistant. The conservation of the plague bacillus in the earth of the burrows must be able to occur at least temporarily (without prejudice to the influence of different soils, their pH, etc.) everywhere, as one of us has demonstrated (10) by isolating this bacillus from relatively shallow burrows of M. vinogradovi. But all unoccupied burrows are doomed without delay to disappear; the enormous reservoir of plague which they contain is thus rapidly and definitively buried. In fact, it could not be maintained that, whatever the rate of reproduction of rodents at the apogee of reproduction, and whatever the density of "dead" burrows during the preceding epizootic outbreak, the new arrivals have much chance of encountering, as they dig their burrows, the tunnels and chambers of their predecessors, which, moreover, would long ago have collapsed under the action of plowing and weather. A special instinct would be necessary, which observations within the area we have been observing for five years have never shown us.

It is, therefore, certainly only in burrows which will continue to be inhabited during the inter-epizootic period that susceptible rodents will be able to encounter again infected soil (which has no effect on resistant rodents inhabiting such burrows), when the push of their reproduction will bring them again into contact with the populations of these resistant rodents. It seems probable, according to observations made in nature, that the conservation of the germ during

the long duration of the inter-epizootic periods can only occur in the large permanent burrows, the deepest ones, which provide the most stable microclimate: that is, in Kurdistan, the burrows of M. persicus and M. libycus. In fact, it is in these burrows that, when the current epizootic outbreak is over and the disappearance of the plague among the rodents and their fleas will have again been proved, that we shall have to seek the presence of infection in the soil of the deep chambers where we already know that we ought to find, mingled with the litter of the surviving meriones, the debris of the dead meriones.

How are we to picture to ourselves the cycle of this telluric plague? It appears that our previous researches in the region studied unknowingly showed its mechanism. At the close of an epizootic outbreak, 95 percent of the burrows have been subjected to infection: it is easy to see this in the populations of the susceptible rodents, among which residual "islands" which escape the plague are rare and scattered. However, in populations of resistant rodents, although the potency of contamination, further reinforced by the hecatombs of susceptible rodents infiltrating those populations, has overcome the resistance of many rodents which died of the infection, some of the burrows continue to be inhabited by the surviving ones, of which our current estimates fix the number at more than 30 percent. Even before the end of the epizootic outbreak, as soon as its violence begins to falter, the "dead" burrows begin to be reoccupied by the resistant survivors, and subsequently, under the influence of the rapid multiplication of these rodents, all those "dead" burrows which have not disappeared will be reoccupied by these survivors or their descendants. In at least one chamber of each of these burrows are heaped up the cadavers of the animals killed by the epizootic outbreak. It is beyond doubt that the plague bacillus could not be systematically conserved in all these burrows; the few researches which have been made in the field, or the experiments which we are pursuing in our climatized dark room seem to show that this conservation is far from being the rule. No matter how rare this conservation may be, however, it is is the thousands that burrows which are reservoirs of plague must be numbered.

Meanwhile, it is from the very small number of susceptible rodents spared by the epizootic flood tide that the repopulation of their territory begins. However, their prolificity more or less quickly leads to enormous multiplication, in accordance with always visible climatic conditions, sometimes after more than two years, as shown by our most recent observation. We think that we have clearly demonstrated (4) that this multiplication pushes these susceptible rodents to invade the microfoci of resistant rodents pushing them back towards the center of their population areas. It is at the end of the last spring of the inter-epizootic period, at the time when reproduction achieves its maximum, and when the young ones are cheerfully seeking their own establishments, that there occurs the contact between susceptible rodents and the plague in the burrows, and we have been able

to prove experimentally that it must be sufficient for one of these rodents to explore an infected burrow for only a few moments to be contaminated (19). Since the phenomenon occurs at the same time at the level of many microfoci, it explains the particular aspect of the appearance of the plague which we were able to observe in the "mesofocus" which we are continuing to study (5). In this mesofocus, the major role in the conservation of the plague falls to the burrows of Meriones persicus, because of their numerical superiority. In relaunching the infection, the major, if not the only role is that of Meriones tristrami -- the most mobile, and most audacious, the most competitive, and the first to enter the territory of M. Persicus under the impulse of reproduction; this M. tristrami is at the same time the most susceptible, subject to extraordinarily rich septicemia, but it also has the fewest fleas. Moreover, this merion's mobility carries it from the infected burrows of M. persicus to the populations of M. vinogradovi, and it appears that it unleashes the plague at the same time in the two habitats. The M. vinogradovi, very numerous, established in large populations, rich in fleas, very susceptible to infection, will launch the epizootic process; the M. persicus, in small groups of burrows, less dense and more scattered, will, largely because of their resistance, become infected more slowly, but will also conserve it longer in the same places.

What may be the importance of this telluric plague? When we defined the burrowing plague as "a major mode, susceptible of being regarded as a habitual mode of contamination in nature" (19), we were certainly not thinking of questioning Simond's discovery and the classic cycle of rodent-flea-rodent. We could not imagine, and still less claim, that the plague bacillus is a saprophyte of the soil, from which it emerges to encounter, through an accidental cycle, "epizootic chance" and more accidentally still "epidemic chance"; neither are we close to going back to the ancestral concept of plague coming from cemeteries by disinterring corpses. However, we recognize two possibilities of existence for the plague. One through the classic cycle vertebrate-flea--vertebrate, the instability of which we believe all researchers are agreed upon, even if this instability may, as we wrote concerning temporary foci (1), maintain equilibrium of infection for more than a half century. The other by conservation in the soil, whose duration in nature we do not know, but which may be longer and more stable than we imagine: sixteen months in a laboratory jar certainly indicates much longer periods in burrows. The two modes follow one upon the other, and are interlinked [see Note], and in our opinion only the fact of their being interlinked can create longevity of plague. In inveterate foci, one cannot exist without the other: if the enormous mortality of the epizootic outbreak did not periodically "recharge" the plague reserve of the burrows, the infection would sooner or later die out; if the plague reserve in the ground did not exist, the rodent-flea-rodent cycle would be broken, as always happens sooner or later in temporary foci.

Nature's action has, therefore, created that "safety reserve" the concept of which is due, indisputably, in our opinion, to Georges Blanc, a concept which we have so often discussed with him, and which has led us, little by little, to the following working hypothesis. Strict parasitism, that is, in which the parasite cannot live outside its hosts or vectors, is only the most evolved form of that mode of life; the further we go down the scale of living beings, the rarer parasitism is: at the level of mushrooms, bacteria, and viruses, it becomes the exception. It is possible, therefore, that the best known cycles of strict parasitism, which appear to us to be complete, may only, in reality, be a phase of the true cycle, in which an extra-parasitory stage might exist. This stage would be characterized by extreme resistance in nature, and by considerable reproduction and "waste" which is always found whenever the danger of chance intervenes in the continuity of the cycle. This stage ought to be systematically sought, for even in cycles in which its existence does not appear necessary; in accordance with phylogenic logic, this research ought to deal with the precise milieu in which it may be supposed that the being lived free before adapting to parasitic life.

So far as the plague is concerned, we abandoned this concept long ago; our researches have brought us back to it. The waste of means in inveterate foci is obvious, doubtless because the role of chance is greater there. We can define this role of chance: we have said that in the overwhelming majority of infected burrows it appears more than probable that only a limited number will conserve plague; the visits to or usurpations of these burrows by susceptible rodents will, even during the peak of pullulation, be a certain, bur rare, occurrence; finally, even in infected burrows, it is quite certain that the chance of contamination of these visitors or usurpers do not equal those we achieved in our experimental jars. Consequently, the enormous waste of the means employed will result in a small number of successes; that, in fact, is very precisely the picture shown us by the outbreak of plague in 1962 (5).

Are these working hypotheses, the guidelines of our future researches, applicable elsewhere than in the foci where we got the foundations for them? According to all probability: yes. To our knowledge there exists nowhere in the world an inveterate focus where there are not one or more sedentary species with deep burrows, burrows more or less frequented by other species. As an example, we shall give only the single one which we learned about by ourselves: that of the region to the east of the Caspian Sea, part of the vast central Asian focus, according to current Soviet terminology, the southern part of which we have studied in Iran (Gorgan-Dach Boroun region), without, moreover, finding the plague, which, however, used to be know in those regions. There <u>Meriones libycus</u> is certainly much more susceptible (as is proved by the history of the so-called Turkoman epizootic outbreak in 1953-55) than <u>Rhombomys opimus</u>, as the Soviet authors observed during the same

epizootic outbreak, and as we were able to see experimentally on the M. libycus and Rhombomys of Dach Boroun. Now, if Rhombomys dig deep, permanent burrows on hillsides, while M. libycus are established in shallow burrows on flat, low-lying land, the intermingling of the species is such that traps set in front of Rhombomys burrows often yield more M. libycus than Rhombomys.

The extreme flexibility of nature's means in the face of every kind of condition must, during the course of ages, have permitted the establishment of all the possible combinations between sedentary species with fixed burrows and non-sedentary species. Here we must use the word sedentary in its narrowest sense, and apply it only to rodents inhabiting the same burrows for many generations. In Kurdistan, for example, the M. vinogradovi and M. tristrami, which, however, cannot be termed non-sedentary, constantly change the location of their burrows under the combined influence of plowing and of the plague, and it is to these constant changes that we think we can attribute the conservation of their susceptibility to infection, since they are subjected only to periodic, brutal assaults, and not the continuous and doubtless moderate pressure exercised by telluric infection.

This proposition, however, does not have a converse, and the existence somewhere of wild rodents with permanent, depp burrows is not sufficient for inveteration of the plague: too many factors are involved, including primarily climatic factors, for the conservation of the plague in burrows to be considered a universal phenomenon. In India, for example, where we have given proof of the resistance of the jumping mouse Tatera indica (although its resistance is moderate [3], that is, genetically speaking, limited to a low percentage of the animals captured), it seems improbable that this mode of persistence of infection can be a factor, in spite of the great depth of the burrows of this species and its sedentary nature. Moreover, the inter-epizootic intervals or off-seasons are extremely short, not exceeding the approximately four months of the rodents' estivation, and the flea Xenopsylla astia stands this estivation perfectly well; moreover, infection manifestly does not become inveterate in this type of focus anywhere, which has allowed us, in spite of the long, uninterrupted history of plague in the Ganges valley, to put forward the view that that was not an instance of an inveterate focus, and to forecast the disappearance of infection from that region, a disappearance which has now taken place.

Consequently, research into resistance to the plague among rodent populations with permanent burrows in inveterate foci, or among species frequenting those burrows, seems to us to maintain all its interest. This research is not yet easy: in the hands of the same experimenters, results vary with the identical techniques, according to the sources used, as, for example, Lévi and his collaborators, tell us in their work on the receptivity of Citellus pygmaeus (14).

We believe that difficulties of this type may be resolved by using a source with low pathogenicity, like the source TKR 159, which we have already sent to several of our correspondents. Without necessarily using the delicate technique we employ (bites by infected fleas), this source permits reproduceable results by all methods, particularly percutaneously and subcutaneously, under equal conditions of [illegible] and density of suspension, and can show, since it kills only the rodents most susceptible, any resistance to plague, no matter how weak. The interest of this research into resistance to the plague among the rodents of each focus seems to us to consist in the possibility of authentication of the inveterate character of a focus, an authentication which may assume great importance if it is demonstrated that this inveterate character is linked to the conservation of the plague in the world. It seems, in fact, that simple methods such as flooding burrows with antiseptic liquids, for example, might permit an efficacious attack on the infection at the stage where it is most fixed and most stable, but also most vulnerable.

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