The central ganglion of the tick is not as hospitable to *B. turicatae* as it is to *B. duttonii*.

Brumpt and Brumpt (124) and Mazzotti (483) demonstrated that mice, rats, guinea pigs, cotton rats, rabbits, pigs, dogs, cats, and foxes can be infected with *B. turicatae* in the laboratory but not hedgehogs and dormice. The virulence for guinea pigs is low.

*O. turicata* cannot transmit *B. duttonii, B. venezolensis* (118), or *B. dugesii* Mazzotti 1949 (228).

### *Ornithodoros parkeri and Borrelia parkerii*

*Ornithodoros parkeri* Cooley 1936 transmits *Borrelia parkerii* Davis 1942. It lives in the western region of Canada and the United States but not in Mexico, in caves and burrows inhabited by ground squirrels, prairie dogs, and burrowing owls (384). It only infrequently encounters man. The infection is transmitted by the bite of the tick because coxal fluid is excreted only after feeding. Rafyi *et al.* (593) described a variant of *O. parkeri* that was found on the Hastings Reservation in Monterey County, California. The *Borrelia* harbored by this variant differed antigenically from the type strain.

*O. parkeri* can be infested with *B. turicatae* but not with *B. venezolensis* in the laboratory (485).

### *Ornithodoros hermsi and Borrelia hermsii*

*Ornithodoros hermsi* Wheeler, Herms, and Meyer 1935 was described in 1935, together with the *Borrelia* strain carried by it (730). It was found in the Californian mountains at an altitude between 5,000 and 8,000 ft, but human cases of borreliosis were discovered also at 3,000 ft. It is a disease acquired by persons entering newly opened wooden summer cottages which are frequented (when empty) by wild rodents such as *Tamiasciurus douglasii* and *Eutamias* that often carry this tick in their fur (358).

*B. hermsii* has been studied extensively by Wheeler (727, 728, 729). It is transmitted with the eggs but less than 2% of them are infested. *O. hermsi* does not extrude feces or coxal fluid during feeding. Its bite is infective. When mammalian blood is not available, *O. hermsi* may feed on other ticks. Mice and monkeys can be infected with *B. hermsii* (727). Three days after a meal on an infected rodent or man, the celomic cavity becomes invaded, and



the central ganglion by the 10th day (728, 729). Longanecker (458) found *O. hermsi* in dead trees ("snags") at an altitude of 6,000 to 8,000 ft. Of 39 batches of *O. hermsi*, 18 infected mice, rats, and chipmunks.

### *Ornithodoros talaje and its Borreliae*

*Ornithodoros talaje* Guérin-Méneville 1848 probably has substrains. It is principally a Central and South American tick, found on the West Coast of the Americas and in Argentina. Bates *et al.* (68) observed *O. talaje* in the Arriján area of Panama. Human infections were present there. Rats, mice, and *Macaca mulatta* monkeys could be infected by the bite of *O. talaje*. Dunn and Clark (248) described natural infections in marmoset monkeys *(Sanguinus geoffroyi), Cebus capucinus,* opossums *(Didelphis marsupialis etensis),* armadillos *(Dasypus novemcinctus fenestratus),* cattle, and in a horse. *O. talaje* transfers borreliae rather from animal to animal than from animal to man (182, 222) even though it often appears near human habitats (89). It attaches itself to opossums and other animals that prowl around horses and cattle tied to bush fence posts in which *O. talaje* then finds a home. It may also crawl under houses.

Vampire bats and *Triatoma* bugs may acquire this *Borrelia* but do not transmit it to other animals. Some strains of *O. talaje* do not bite man (222, 577). The *Borrelia* transmitted by *O. talaje* has not yet been named because it was believed that it is identical to that from *O. rudis*. Matters became complicated when Calero (137) stated that *B. neotropicalis* is a variety of *B. recurrentis* carried by *O. venezolensis* (synonym: *O. rudis)* as well as by *O. talaje*. Mazzotti (484, 485) found incongruities between the bionomics of *O. venezolensis* and *O. talaje* on one hand, and *B. venezolensis* on the other hand. Davis (225) stated that *O. dugesi* is a possible alternate host of *B. talaje*, and described *B. mazzottii sp.nov.* from *O. talaje* from Mexico and Guatemala that transmitted this *Borrelia* regularly, and *O. dugesi* weakly and in a fleeting way. *O. talaje* from other areas (Panama) did not transmit *B. mazzottii,* nor did *O. venezolensis, O. turicata* from Mexico, and some other ticks. There was no transovarian passage in *O. talaje* carrying this *Borrelia.* Guinea pigs and young rabbits were refractory to it. Considering

further that *B. venezolensis* (synonyms: *B. venezuelensis* Brumpt 1924, *B. neotropicalis* Bates and Saint John 1922) is present in *O. rudis* Karsch 1880 (synonyms: *O. venezuelensis* Brumpt 1921 and *O. venezolensis)* in approximately the same area, and that the differentiation of borreliae by immunologic and serologic means is most difficult, one could assume that *O. talaje* carried *B. mazzottii* and in addition a hitherto unnamed *Borrelia,* the vector being perhaps a subspecies of *O. talaje.* Further investigation of this problem is certainly indicated and, until such studies are carried out, one has to keep an open mind.

### *Ornithodoros venezolensis and Borrelia venezolensis*

The synonyms were discussed under *O. talaje,* which is said to be able to carry also *B. venezolensis.* Pifano (573) found this tick in Venezuela and in Mérida on the Yucatán (Mexico). A "related" tick was discovered in Yayacuy. The tick acquired the habits of a bed-bug, and became domesticated. Rats and mice on which the tick was fed developed borrelemia. The *Borrelia* was neurotropic. No animal reservoir was found. The ticks appeared to feed only on man, as shown by precipitin tests with sera against various animal blood. Osorno Mesa (558) found *O. venezolensis* in Santander, Colombia, and suspected that human cases may exist there. Anduze (18) collected *O. venezolensis* in the Mérida area of Venezuela at an elevation between 1,600 to 5,000 feet. The human relapsing fever caused by its bite was severe. León and León (443) found the vector in Esmeraldes, Colombia, and varying clinical pictures of the disease. They suspected birds and wild rodents as the reservoir. Mazzotti (484) believed that *B. venezolensis* is the causative agent of relapsing fever in Panama, Colombia, and Venezuela, that *O. talaje* and *O. venezolensis* carry it, but perhaps that the strains are diffenent.

### *Other Borreliae*

*Ornithodoros brasiliensis* Argão-Beaurepaire 1923 carries *Borrelia brasiliensis* Davis 1952 (224). This tick has one larval and 4 to 7 nymph stages before the adult emerges. It is able to feed two days after moulting. Davis was the first to rear these ticks in the laboratory. Little information is available about the disease



caused by *B. brasiliensis* and the ecology of the ticks. It appears, however, that *B. brasiliensis* can be transmitted to mice and guinea pigs.

Heisch (345) described *Ornithodoros graingeri,* the vector of *B. graingeri* Heisch 1953 in Kenya. It caused disease in man, with slight neurotropism. The illness was mild in rats and mice. Guinea pigs, young rabbits, and monkeys were not susceptible.

Garnham (293) reported a *Borrelia* from a grivet monkey.

Carley and Pope (144) described *Borrelia queenslandica* from *Rattus villosus* in Australia. It caused relapses in mice and rats. Guinea pigs and chickens were not susceptible. This *Borrelia* could be carried in the laboratory in fertilized chick embryos. It was not transmitted by *O. gurneyi,* the only *Ornithodoros* species in the area where the organism was isolated.

Further data are not available on these borreliae.

### *Other Ornithodoros*

*Ornithodoros coniceps* Canestrini 1890 was considered a possible vector of borreliae but Chagin and Diatlov (151) demonstrated that it is not infected in nature. However, about 2 to 3% of these ticks will take up *B. persica* when fed on infected animals, and will transmit this *Borrelia* to about 10% of the guinea pigs on which they are fed at a later date. Ovarian transmission has also been observed.

*Ornithodoros lahorensis* Neumann 1908, which was said to be a vector, was unable to transmit Central Asian borreliae in the hands of Pavlovskii and Kuzima (567). *O. lahorensis* is common in the stone walls of old caravanserais, in cracks of wooden buildings, and in sheep stalls. Perhaps it lives also with rodents in their burrows (584).

*Ornithodoros foleyi* Parot 1928 (synonym: *O. franchinii)* was considered a vector of *B. hispanica* in Lybia where two war-time louse-borne epidemics raged. Colas-Belcour and Vervent (191) were unable to prove that it plays a role in the propagation of relapsing fever.

*Ornithodoros savignyi* Audouin 1827 has been observed from Timbuktoo to Ceylon. It has never been found to be infected in nature although it takes up *B. duttonii* and *B. hispanica* in the

laboratory (121). Considerable research has been devoted to this tick which lives outdoors, especially in places where camels, sheep, and other livestock rest. The reason is that it appears in areas where relapsing fever is present but generally accepted tick vectors are scarce, sporadic, or have not yet been found. One of these countries is Somaliland. Moise (497) suspected but did not prove that *O. savignyi* is an effective *Borrelia* vector. Kirk (410) could not transmit *B. recurrentis* to it in Abyssinia. Walton (710) showed that *O. savignyi* is a pure field tick. Lovett (461) in Somaliland found *O. moubata* to be a potent vector, but still believed that *O. savignyi* may participate in the dissemination of relapsing fever. Anderson (16) pointed out that *O. moubata* lives mostly indoors and has much more intimate contact with man so that it must be a much more effective vector.

*Ornithodoros canestrini* Birula 1845 was investigated as a possible vector of borreliosis by Delpy *et al.* (236) in Iran but neither *B. persica* nor *B. microti*, the borreliae of Iran, could be transmitted by this tick in animal experiments.

**Unusual Vectors**

A number of arthropods other than human lice and *Ornithodoros* have been considered as possible vectors of human relapsing fever. Bedbugs *(Cimex lectularis)* are the first in importance among these.

Rosenholz (611) surveyed the literature and in his own experiments found *B. duttonii* in the gut of bedbugs for 5 days after feeding, but borreliae did not find their way into the celomic cavity in all the bugs that were fed. *B. duttonii* survived for about 2 months in those that were successfully infested. Chung (172), studying an outbreak of epidemic relapsing fever in an orphanage in Peiping, stated that bedbugs may acquire *B. recurrentis* but the organism vanishes from their blood in one day. Furthermore, Chung and Feng (178) concluded from the results of their experiments that bedbugs, like lice, have to be crushed to transmit the infection. Francis (278) succeeded in transmitting *B. turicatae* by *C. lectularis*. Bonné (100) stated that while bedbugs and *Melophagus ovinus* can harbor borreliae for about 2 days after feeding, they do not transmit the organisms to mammals. Blanc *et al.* (82) observed considerable differences in the survival time of borreliae



in bedbugs according to the microbial strain employed in the experiment. *B. hispanica* could be detected for 2 days, *B. persica* for 3 to 48, *B. duttonii* for 150, and *B. merionesi* for more than 200 days after infestation. The virulence of the borreliae did not diminish during their sojourn in the bedbug. Weyer and Moser (726) were able to preserve *B. recurrentis* and *B. hispanica* in frozen bedbugs.

The South American *Cimex rotundatus* was considered a possible vector of *B. venezolensis* by Pino-Pou (577).

The dog tick, *Rhipicephalus sanguineus*, has been another object of numerous querries. Sergent (637) found this insect, infected, on a dog belonging to a patient with relapsing fever in North Africa. Sergent (639) later reviewed the literature on this subject. Bonné (100) observed infected larvae. When the infective meal took place during the nymph stages, the adult *R. sanguineus* carried borreliae for about 3 months.

Members of the tick genus *Argas* are transmitting fowl borreliosis. It is natural that their relationship to human relapsing fever has also been investigated. Bonné (100) was unable to transmit African borreliae by *Argas reflexus*. Harold (337) asserted that *Argas persicus* does not bite man and is, therefore, not a probable vector of human relapsing fever.

The tropical rat mite *(Liponyssus nagayoi)* was studied by Omori (554). It transmitted *B. duttonii* from mouse to mouse for 12 days after the infective blood meal. Its feces and ova remained free from borreliae.

Fränkel (280) attempted to transmit epidemic relapsing fever from man to man by the stable fly *(Stomoxys calcitrans)*. This fly, as many other biting insects, is able to harbor live borreliae in its gut for a few days but cannot transfer the organisms to man.

It is possible to paraphrase an axiom by saying that several borreliae may be looking for a vector, and several vectors for feasible hosts. Potential rodent reservoirs without active carriers of borreliae exist in several parts of the world. Huang (375), for instance, enumerated *Microtus mandarinus, Cricetus triton, C. barabensis, Micromys minutus*, and *Apodemus agrarius*, rodents living in the Yang-tse Valley in China, which represent such a potential reservoir. The disease is absent, however, principally because of the lack of an efficient and infected tick vector.

## Portals of Entry

Transmission of borreliae takes place most often during the feeding of anthropophilic vectors of human pathogenic *Borrelia*.

During gestation, borreliae seem to be transmitted from the blood of the mother to the fetus (19), but the organisms are not transmitted through the milk to the offspring (292, 602). Infection may be acquired from the nursing mother, however, through mucous membranes (73). Menstrual blood also carries *Borrelia* (116). Skin excoriations as well as intact mucosal membranes may serve as portals of entry (54, 107, 364). Chung (174, 175) in China, observed that human urine and prostatic fluid may harbor borreliae. He was able to transmit the organisms to susceptible animals in the laboratory.

Laboratory infections have been described as having originated with human clotted blood kept for six days at room temperature (464), infected monkey blood (642), blood from the vein of a patient which squirted into the nose of a technician (429), and in one case, infection occurred in a laboratory worker who accidentally splashed patient's blood into his eyes and in another who was sprayed accidentally with placental blood (462). A classical example of a laboratory infection is that of an entomologist who was contaminated with the blood of a squirrel he was dissecting (442). Borreliae may be transmitted also with blood transfusions (596, 716). These are rare exceptions, however, and the classical route is infection by a feeding human louse or *Ornithodoros*.

## Attempts to Classify Borreliae According to Response of Experimental Animals

The reader may have experienced considerable difficulties in perusing the preceding pages when attempting to sort out the various hosts or when sifting out the responses of experimental animals in the laboratory to infections with the different *Borrelia* strains. This author has to admit that the study of many of the individual reports quoted in this monograph was not always an easy task, for details of technics, of the mode of infection, the age and condition of the animals including their stock were not always made clear in some writings on this subject. The re-testing of many data is still a prerequisite for the formation of a clearer picture of the parasite-host relationship under laboratory conditions. This can be done by checking available reports by experimenting with accessible *Borrelia* strains and standardized methods. A critical evaluation of the procedures hitherto employed needs to be programmed by keeping in sight two goals: first, the ability of the vector to infect a given animal species. The results of such investigations will help to delineate the animal reservoir, the possible formation of biotopes, and therewith, assist in obtaining information useful from the epidemiologic point of view. Secondly, the question has to be answered whether a *Borrelia* separated from its vector and administered to a laboratory animal will or will not cause signs and symptoms valuable for the laboratory diagnosis of the strain.



Transmission by vectors has been discussed in the foregoing chapters, and will be analyzed again in the portion of this monograph dealing with epidemiology. At this point we are concerned with the susceptibility of laboratory animals, and with the possibility of their use in the classification of *Borrelia*.

Mice have been used for a long time in experimental borreliosis.

They are small, easily maintained, and usually on hand in larger laboratories. There is, however, the question of the route of inoculation, and the age and strain of the mice. Gray (322), for instance, stated that young mice are more susceptible to *B. duttonii*. Kemp *et al.* (406) found that mice are easily infected with North American borreliae. Wolman and Wolman (736) confirmed the susceptibility of mice to *B. recurrentis*. Coghill and Gambles (186) were able to produce short-term disease in mice by inoculating them with the blood or brain from patients in whom *B. recurrentis* could not be found by other methods in the peripheral circulation. Baltazard and his group (46, 59, 60, 61) emphasized the feeble but very constant susceptibility of mice to *B. recurrentis* and other borreliae. Baltazard (47) also demonstrated that the time of borrelemia in mice could be prolonged by splenectomy from the usual 3 days to a longer period. Kroó (425) emphasized that the virulence for mice varies with the strain of the *Borrelia* and with the relapse from which the infective material was collected. Durieux and Boiron (249), in their studies of relapsing fever in Dakar, used mice as indicators for their survey

of the occurrence of borreliae in naturally infected animals, injecting the blood of such animals into laboratory mice.

Geigy and Aeschlimann (300, 305) showed that *B. duttonii* causes more persistent infection in mice than *B. recurrentis.* Sergent (638) reported that mice become ill 24 hours after inoculation with *B. hispanica* but recover after a short period.

Young mice were preferred and recommended by Geigy and others (300, 305, 662, 663) for laboratory experiments with borreliae. Guggenheim and Halevi (329) demonstrated that thiamin-deficient mice become more seriously ill than well-nourished mice when infected with borreliae.

Baltazard *et al.* (46, 59) found the response of adult rats to *B. recurrentis* somewhat variable even after splenectomy, but the borreliae were more pathogenic than they were for mice. Newborn rats became consistently infected, and the borreliae circulated longer in their blood than in the blood of mice according to these investigators (48, 99) who also preferred rats to mice because of their size and the ease with which they can be handled. Rats usually survive the infection, even though they may appear ill. Geigy and Aeschlimann (305) observed that *B. duttonii* is pathogenic but somewhat less for rats than for mice. Kalajew (393) found that splenectomized rats harbor in their circulation enormous numbers of borreliae with a long period of survival of these organisms in the brain. Rats are highly susceptible to the American strains of *Borrelia* (406, 407).

Rabbits appear more difficult to infect. Nicolle and Blaizot (532) had to inject large numbers of *B. recurrentis* intravenously to observe borrelemia lasting 2 days. Sergent (638), using *B. hispanica,* found only few organisms and these only for a short time in the rabbit. Geigy and Aeschlimann (305) recorded rabbits as not sensitive to *B. duttonii.* Greiner (324) succeeded in infecting young rabbits with *B. hispanica.* Baltazard *et al.* (61) were able to produce fatal infection in newborn rabbits, principally after animal passage.

Guinea pigs have developed into a favorite tool for differentiating borreliae. Greiner (324) found them refractory to *B. recurrentis.* Wolman and Wolman (736) observed, however, that guinea pigs could be infected with the Ethiopian strain of *B. recurrentis.*



Baltazard (46) pointed out that these rodents are only exceptionally susceptible to *B. recurrentis.* Coghill and Gambles (186) found that *B. recurrentis* causes only latent infection in guinea pigs, that *B. hispanica* always produces patent infection, and that these animals are refractory to South American borreliae. Kervran (409) observed elevated temperature in guinea pigs after injecting infected blood containing *B. duttonii.* Newborn guinea pigs may be more susceptible to *B. duttonii* (304). Sergent (638) produced a disease in these animals with *B. hispanica* starting with an acute attack, then becoming chronic. Colas-Belcour and Vervent (191) made similar observations. Davis (219) found guinea pigs susceptible to all North American strains of *Borrelia.*

Baltazard *et al.* (62) suggested the use of guinea pigs in the differential diagnosis of borreliae because they are highly susceptible to *B. hispanica, B. persica,* and, principally young individuals, to North American strains but not to *B. latyschewyii,* the crocidurae subgroup, and in most instances not to *B. recurrentis.* Adults, however, were refractory also to *B. duttonii* in his experience.

Different species of monkeys and apes have been found to be susceptible to various species of borreliae. Nicolle and Blaizot (532) produced transient infections in hooded monkeys with all strains of *B. recurrentis. Macaca sp.* was particularly susceptible to the Tripoli strain of relapsing fever. LeGac (439) and Baltazard (46) also observed that *Macaca* and *Cercopithecus* monkeys could be infected with ease. A mild disease resulted. *Cynocephalus* was refractory to his *B. recurrentis* strain. *B. duttonii* may cause fatal infection in monkeys (303, 304). Rhesus monkeys have been found susceptible to North American *Borrelia* strains, also to South American borreliae (68). *M. inuus* became infected with *B. hispanica* (99, 638) but minimal pathogenicity of the crocidurae subgroup was observed in *Cynocephalus.* We have found patas *(Erythrocebus patas)* mildly susceptible to North American borreliae (268). The incubation period varies according to the mode of inoculation.

Dogs have been used by Sergent (638) in the study of *B. hispanica.* Young animals were easily infected.

Chickens were recommended for experimental purposes by Kervran (409), who transmitted *B. duttonii* to them.

Hamsters have been little used in *Borrelia* experiments. Chen and Anderson (159) found them susceptible to *B. hermsii.* We were

able to transmit *B. turicatae* and *B. parkerii* to them. Splenectomized hamsters infected with *B. recurrentis* were studied by Chen *et al.* (160), who saw mild disease.

Cotton rats *(Sigmodon hispidus)* were found by Varma (701) to be more susceptible to *B. turicatae* infection than were white mice.

The possibility of using the European hedgehog *(Erinaceus europaeus)* as an experimental animal was studied by Lapierrre *et al.* (435). The hedgehog was resistant to *B. duttonii,* acquired an inapparent infection when infected with borreliae of the crocidurae subgroup, was susceptible to *B. hispanica,* and became seriously ill after infection with *B. persica.* However, the response was not always clear-cut and varied with the strains of the respective species.

Some animal experiments have been carried out by unorthodox routes of inoculation.

The infection of white rats by the transnasal route, using *B. hispanica,* was successfully accomplished by Nájera Angulo (514). Joyeaux and Sautet (389) infected rats by feeding them with brains of other rats infected with *B. duttonii.* Conjunctival and peroral infection of squirrels with *B. recurrentis* was accomplished by Chung (172). Blanc *et al.* (83) produced *Borrelia*-keratitis in the rabbit eye. *B. hispanica* caused a lesion resembling syphilitic keratitis, whereas *B. duttonii* and *B. merionesi* evoked different pathologic pictures.

Chorine and Crogue (168) quantitated *B. hispanica* in guinea pigs. The multiplication of borreliae in experimental animals was also studied by Eidmann *et al.* (252) and Baltazard *et al.* (57).

Reinfection of susceptible animals is possible after several months (533, 546).

Summaries of borreliae in laboratory animals may be presented as follows. Nicholle and Anderson (526) stated that:

1. *B. duttonii* and its relatives are virulent for mice and rats, hardly at all for guinea pigs.

2. The *B. hispanica* group is equally pathogenic for mice, rats, and guinea pigs.

3. Small-rodent borreliae can infect mice but rats and guinea pigs are not sensitive. Members of this *Borrelia* group are mildly harmful or nonpathogenic for man.

Geigy (303) summarized:

1. *B. recurrentis* causes infection in monkeys, usually after 2 to



4 days' incubation, with borrelemia lasting about 4 days. Adult mice and rats are not very susceptible, developing borrelemia with various intensity. There is no residual brain damage in the infected animals.

2. *B. duttonii* is strongly pathogenic for guinea pigs, monkeys, rats, and vervets.

3. *B. hispanica* and *B. turicatae* may cause disease in guinea pigs, but some are refractory. Monkeys, rabbits, rats, and mice can be infected while young.

4. *B. venezolensis* infects rats and mice but as a rule not rabbits and guinea pigs.

We would like to emphasize that the severe response of monkeys to *B. duttonii* and that of guinea pigs to *B. persica* and *B. hispanica* are valuable laboratory aids in differentiating tick-borne Old World borreliae.

Perhaps more extensive studies are needed on animals that harbor certain borreliae in nature or become occasionally infected with them. After standardizing the route of infection, the age of the animals used, and the infective dosage, the differentiation of *Borrelia* strains may become an easier task in the laboratory.

### The Interference Phenomenon

Trautmann (689) is said to have been the first to experiment with *Trypanosoma* and *Borrelia* on the same animals in 1907. He noted that rabbit serum against *B. duttonii* immobilized but did not agglutinate *T. brucei* and *vice versa.* Daels (214) confirmed these observations. Vassiliadis and Jadin (702) found that *B. hispanica* slows down *T. rhodesiense* infections but to a lesser degree than *B. duttonii* mitigates the disease caused by *T. pecaudi.* Rubinstein and Kapusto (615) believed that a new, symbiotic "race" of *Borrelia* may develop in mice in mixed infections. Kawamura (400) reported that the injection of *B. duttonii* and *B. hispanica* simultaneously causes prolonged infection in mice but that the administration of *B. hispanica* or *B. crocidurae* together with *T. brucei* prolonged the life of the mouse from 3 or 4 days to about 22 days. Vincent (707) observed that when *T. somaliense* and *Borrelia* were injected simultaneously, the incubation period was the same as when both organisms were administered separately, namely, 3 days for the *Borrelia,* and 2 to 5 for *Try-*

*panosoma*. The *Trypanosoma*, however, multiplied slowly and the mice did not die in 5 to 9 days as usual after injection with *T. somaliense*. The number of typanosomes increased, and began to appear in the blood periodically. Then, *T. somaliense* started to multiply and killed the mice in 30 to 40 days. Vincent believed that the reticuloendothelial system (R.E.S.) played a significant role in these variations of suppression.

Carminati (146) experimented with *B. duttonii* and *T. brucei, T. gambiense,* and *T. equiperdum* in mice. Interference between the *Borrelia* and the *Trypanosoma* strains was observed only while numerous borreliae circulated in the blood. After their disappearance, the trypanosomiasis ran its usual course. The sera of animals treated with *B. duttonii* alone did not show anti-trypanosomal antibodies. Lapierre *et al.* (434) and Larivière *et al.* (436) extended their experimental work to *B. crocidurae;* Lapierre *et al.* (433) to several strains of *B. duttonii, B. hispanica,* and *T. brucei*. Gaillard *et al.* (286) studied also *T. cruzi*.

All investigators found variations in the interference phenomenon according to the strain employed but Gaillard *et al.* (287) felt that this phenomenon could be utilized in the differential diagnosis of borreliae. Mice should be infected with the unknown strain, and *T. brucei* injected at the height of the borrelemia. If the mice survive for a long time (2 or 3 weeks), the unknown strain may be *B. duttonii* or a member of the crocidurae subgroup. If the mice die within one week, the *Borrelia* is *B. hispanica* or *B. persica*. *B. turicatae* gives variable results.

The interference phenomenon may be due to the antigenic and biological resemblance of borreliae and trypanosomes which has been pointed out repeatedly (264, 265).

Borreliae do not interfere, however, with *Spirillum minus* and *Leptospira* infections (262, 465), malaria (640a), *Coxiella (Rickettsia) burneti* (81), or coxsackie B (447) infections. Borreliae show certain cross-reactions with treponemas and *Proteus OX* strains. This will be reviewed together with the evaluation of the importance of such responses for serologic tests in the chapter on Laboratory Diagnosis.

## EPIDEMIOLOGY

Human relapsing fever, a disease carried by specific insect vectors, follows the epidemiologic pattern of arthropod-borne communicable diseases. While numerous additional factors may need to be taken into consideration, our broad outline of an ecosystem in which relapsing fever thrives is as follows.

1. The presence of a sufficient number of susceptible nonimmune persons.
2. An adequate number of an efficient, infected arthropod vector, and suitable conditions for its survival and propagation.
3. Contact of man with such carriers of borreliae.
4. The readiness of the vector to feed on man.
5. The capability of the arthropod to transmit the infectious agent to man.
6. Either the ability of the arthropod to sustain *Borrelia* by transovarian transmission in its own population, or the presence of a satisfactory number of mammals with the faculty of serving as a reservoir of borreliae.

In the foregoing chapters dealing with the history of relapsing fever and lice, *Ornithodoros,* and *Borrelia,* numerous examples have been presented which illustrate ordinary as well as unconventional relationships between man, vector, and often also animal reservoir in certain biotopes. Bionomic factors conducive to novel epidemiologic situations were discussed, for instance the propensity of some *Ornithodoros (O. moubata,* and some American species) to become domesticated, herewith introducing new ecologic elements into the picture. Upholding the basic facts that louse-borne relapsing fever is epidemic, whereas tick-borne is endemic, this chapter will deal separately with the two forms of human borreliosis. Some fundamental features have to be recounted together, however, in an endeavor to create a comprehensive image of the epidemiology of borreliosis as was done by Martini (471), Gelman (315), Geigy (303), and others.

### Epidemic Relapsing Fever

The epidemiology of this disease has been related up to the time of World War II in the chapter on History. Bryceson *et al.* (127) stated that 50 million persons suffered from relapsing fever during the first half of this century, with an average mortality rate of 10%. World War II and its aftermath generated about one

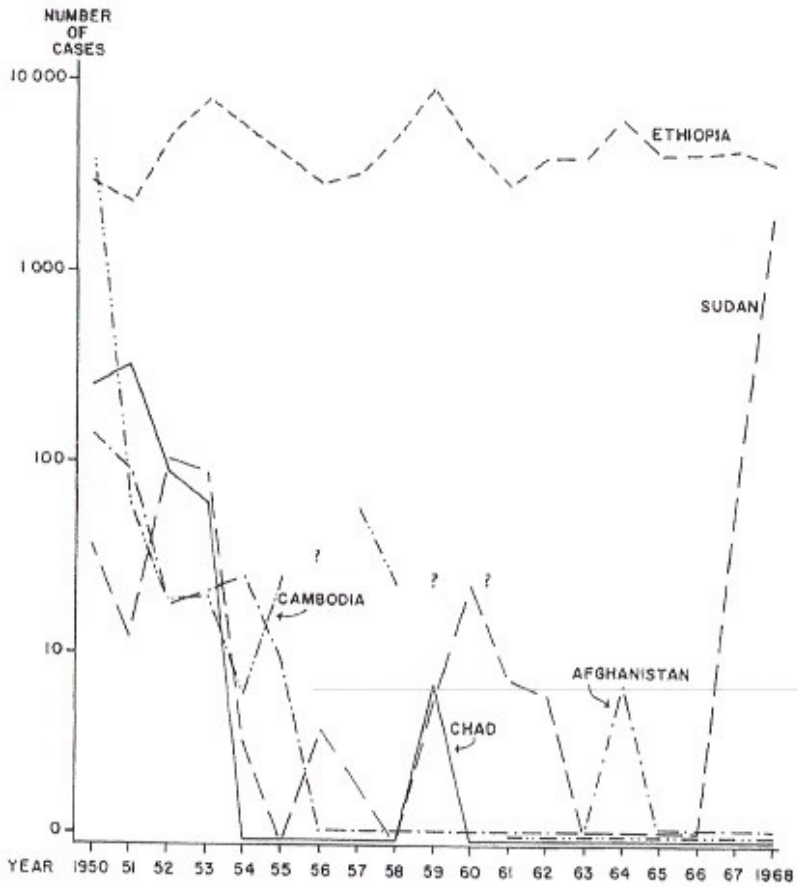


FIGURE 27. Distribution of louse-borne relapsing fever, 1950-1968, according to reports to W.H.O.

million reported infections, with about 9 million unreported cases and a 5% fatality rate, in spite of antibiotics and insecticides. These authors who studied the Abyssinian-Sudanese focus emphasized that no country is without lice. This invites attention to the ever-lasting danger of the expansion of the disease, and of the hazard of formation of new foci.

Epidemic relapsing fever has no other known reservoir than man. Admittedly, the monkey louse may transmit the causative *Borrelia*, and laboratory experiments have substantiated that non-human primates are susceptible to the disease. To the knowledge



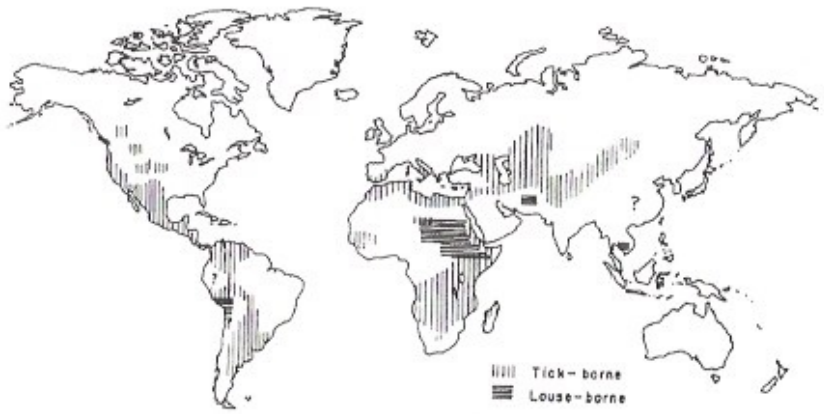


FIGURE 28. World distribution of relapsing fever, 1950-1969.

of this author, naturally infected monkey or ape populations, however, have not yet been reported. Recollecting also that the human louse does not transmit the infection to its progeny and that it has to be mutilated or killed to infect the wound resulting from its bite with celomic fluid containing borreliae, it is obvious that one louse can infect only one person, and therefore an increasing array of *P. humanus* is necessary to create an epidemic. Moreover, the infected lice must have a chance to gain access to a nonimmune person within their rather limited life span in order to transmit the infection. Such an opportunity arises when people are compelled to live in close proximity to one another.

Chung and Chang (176) enumerated conditions under which crowding of people makes it feasible for the transmission from one person to another to take place readily. Army camps, jails, poor houses, orphanages, and similar institutions, if not managed properly, may become centers of relapsing fever. Chiriboga (164) ascribed relapsing fever in Peru to poor housing, especially when living quarters were shared with animals. *P. humanus*, as a rule, however, does not feed on domestic animals. Animal husbandry so to say in the bedroom merely reduces proper hygienic conditions and diminishes living space.

The time for epidemics is the cold season (winter) when people huddle together, and heavy clothing is being worn, in which lice find a feasible microclimate. Accordingly, in hot and humid Cen-

tral Africa the lightly dressed inhabitants escape lice. In Southern India, lice are found only among the very poor. Corkill (202) demonstrated that the time sequence of relapsing fever may be changed. The malady appeared in the spring in Gedaref, Sudan, being activated by kala azar infections. Baltazard *et al.* (63) observed the reappearance of the disease by the end of the winter and considered the possibility that this might have been due to a variant *Borrelia* strain. Several authors (163, 388, 645, 649) have corroborated the parallel between louse population and relapsing fever in China.

The end of the epidemic may occur when heat and humidity become high. Then the louse leaves man. At the peak of the Indian heat, during April and May, the lice begin to die (206, 207).

The seasonal occurrence of relapsing fever may be changed also by migration. Kirk (411) pointed out that migration between Egypt, Sudan, and the former French West Africa was accompanied by the introduction of infested lice. More will be given about this in the discussion of the epidemiology in Abyssinia. Chiao (163) observed also the spread of relapsing fever along highways in China, which resulted in about 5,500 cases among people associated with wayside inns and farmers living along the routes. Lanzo and Tresca (432), commenting on 2,914 cases in the former Erythrea Colony, also saw a shift from the classic winter relapsing fever season to June-September because of the time of labor migration.

People on the move, like migrant laborers, nomads, vagrants, pilgrims, sheep herders, and cattle dealers (260), acquire lice more easily than permanently settled segments of the populace, with the exception of those who live in crowded quarters with insufficient means for good hygienic practices, but including inhabitants of very cold mountainous regions who seldom change their clothing. Old clothes dealers may acquire and spread lice (154). The disease was introduced by this means from Arabia to Kenya in 1945 (296). Persons frequenting markets in which infested clothing is offered for sale, or those who come in contact with louse-carrying animal dealers moving about, also may become infected (260).

On the other hand, nonimmune immigrants entering infected areas, as in Abyssinia, principally seasonal laborers and job-



seekers who live under poor conditions, may acquire *Borrelia*-infested lice, and the disease.

Age and sex susceptibility seems to exist only as far as the opportunity of acquiring *Borrelia*-bearing lice and the mode of crushing them are concerned. It has been mentioned before that in China and South America lice are often popped between the teeth. Some authors believed that borreliae can enter the body only through abrasions (462), others have cited examples of infection through intact mucosae, such as Legge (440) and L'Abbate and Mannino (429) who reported borreliosis developing after instillation of infected blood into the conjunctivae. The presently prevailing belief is that borreliae may enter the human body through uninjured mucosae, including that of the gastrointestinal tract (135) (see also chapter on Portal of Entry). The popping of lice between the teeth may lead to an increased number of relapsing fever infections, principally among adults. The age and sex distribution of migrants favors males as the victims of relapsing fever. Chung and Chang (176) found the ratio of males to females 6 to 1 in China, Bryceson *et al.* (127) 3 to 1 in Abyssinia. The latter authors observed the disease principally among young males, as did Robertson (606) in China.

During wars and other disasters, such as earthquakes, famines, fires, and floods, people are often compelled to flee in masses, and to live in congested quarters. Water is usually scarce, clothing is not properly washed, and conditions become favorable for the multiplication of lice. Then relapsing fever epidemics break out.

The great epidemic of World War II is believed to have started in Fezzan in Southern Tripolitania in 1943, according to Gaud and Morgan (298), where the first cases of the 1912 epidemic were also observed. Nomads of the Megarha tribe were supposed to have harbored the infection. Sparrow (664) pointed out, however, that the disease may have been imported from Abyssinia which was at that time, as was Tripoli, under Italian rule. As a matter of fact, the first patient with relapsing fever in neighboring Tunisia was an Italian prisoner of war (323). The epidemic swept through North Africa in 1943-1945, Egypt in 1945-1946, Ethiopia, Sudan, and Nigeria in 1947-1948, Kenya in 1945, then the Near and Far East (297, 298, 303, 500).

During this epidemic Stuart (670) observed that the disease

was at first mild in Tunisia, Algeria, and Morocco, but later became severe with a 10 to 12% mortality. Gaud and Morgan (298) reported a 50% morbidity rate in 1942-1944. This was probably due to lack of herd immunity because relapsing fever was absent from that area for 25 years. Bryceson *et al.* (127), commenting on the 20-year periodicity of relapsing fever in Africa, remarked that this may be the time needed for a nonimmune population to grow up, or it may be caused by military activities recurring after two decades — in 1903, 1923, 1943.

The actual number of cases in North Africa is unknown. Among those recorded by Graeves *et al.* (323), the mortality varied between 1 and 46% in Tunisia, according to the locality. The disease subsided in Tunisia after 2 years, then invaded neighboring countries. Algeria had a 5% morbidity. To the West, Nigeria reported mild cases imported from Morocco to Dakar and Tiaroye Camp.

Spanish Morocco was infected from the former French Morocco. Between March-July 1945, 168 cases were reported. To the East, Egypt was plagued simultaneously by louse-borne typhus and a relapsing fever epidemic. Halwani (333) and Kamal *et al.* (395) stated that about 100,000 persons became ill. Gaud and Morgan (298) described the spread of the disease to Iran, Jordan, Syria, Aden, and Palestine, where only scattered instances were observed, while Iran and Kenya experienced true epidemics. There were 200 cases in Haifa (332). The disease in Kenya was studied by Heisch (340). The aftermaths of the introduction of relapsing fever from Seihut, South Arabia, to Mombasa, Kenya, by several dhows carrying patients who imported the disease, has been demonstrated by the observation of isolated cases by Ombati and Ojiambo (553). Saglan (621) commented upon the mild outbreak in Turkey. The disease reached true epidemic proportions, however, in Abadan, Iran, in November 1945 to June 1946, with 1,087 cases, commencing after an unusual cold spell. This was the first extensive louse-borne relapsing fever epidemic recorded in Iran. Head lice were found on 88% of the patients, and *B. recurrentis* was isolated from some of these ectoparasites. It is not certain that the small outbreak in Northeast Bengal, with 9 laborers becoming ill, was related to the large World War II epidemic (152).

In Europe, Yugoslavia suffered both from louse-borne typhus



and relapsing fever. Serstnev (644) believed that residual endemic foci may still exist in that country.

Romania had about 4,000 cases according to Gaud *et al.* (297) but Zaharia (744) saw 58 cases daily in 1945 and 1946 in a single hospital. Exact statistics are not available from Poland. Lipinski (453) reported a milder course of the disease than during World War I, with a 0.25% case fatality rate. He ascribed this to prompt treatment with arsenicals.

The epidemic reached Hungary from Rumania in 1945 (570). Eighty to 85% of the cases occurred among gypsies who had been relocated in settlements at that time; one-half of all the ill were in the age group between 10 and 29 years. The case fatality rate was 3.7%.

No data are available from the U.S.S.R. It is possible that the *Febris neuralgica periodica,* misnamed also 5-day fever (101), was actually relapsing fever. Böger (88) observed and correctly diagnosed the disease in German troops in the Southern U.S.S.R.

The World War II epidemic also reached Portugal where isolated cases were seen (578) and Spain where it was called "vagabond fever". Sabalette *et al.* (620) studied 30 cases in Sevilla, and Forteza Bover *et al.* (276) 5 in Valencia. This was the first recorded invasion of Spain by louse-borne relapsing fever.

War-connected relapsing fever may be louse-borne, as it was in Korea among the population infested with DDT-resistant lice (17), but it may be tick-borne as in Israel (420) or in India (165) when troops enter caves and tick-infested shelters.

After the World War II epidemic subsided, Afghanistan reported 138 cases in 1958 and a few in 1964. Afghanistan is mountainous, dry, and cold. Such areas are favorable for relapsing fever. Unfortunately, few (or no) data are available from the Pamir, the Himalayas, and from many of the South American highlands. At the other extreme lies hot and wet Cambodia with 4,216 reports in 1950. The number of cases decreased to 6 in 1954, and a few were reported in 1957 and 1958. Although no accounts are available from Mainland China and North Viet Nam, it is possible that louse-borne borreliae are being imported from those countries to Cambodia. On the other hand, isolated foci in Cambodia may be residua of the epidemics during the first part of