always a possibility (253). Proteinuria was noted (74) practically in all instances early in the disease; Pifano (573) observed it during the later course of the disease. Urinary findings resembling those of nephrosis have been recorded (176, 298, 469).

There is fluid loss (464) due to sweating and fast breathing. Blood urea nitrogen is increased. Plasma Na and K are increased but not constantly; Cl is often low in borreliosis in Abyssinia according to Bryceson *et al.* (127). These authors also noted an increase in gamma globulin, possibly changes in beta globulin, and a decrease of alpha globulins and albumin in some sera.

The "neurotropism" of borreliae has been a constantly recurring puzzle. It may be strain-specific because reports on species-specificity list too many exceptions. The infection of the C.N.S. may be latent (133). Garnham *et al.* (296) found, in louse-borne relapsing fever of Kenya, degeneration of the ganglion cells of the cerebellum without meningovascular changes but stated that glia cell reactions may be extensive. *B. recurrentis* may remain in the C.S.F. for 65 to 69 days (582, 583). Borreliae were found in the C.S.F., in the brain, as well as in brain tumors, in East Africa (590). Increased globulin was observed in the C.S.F. (175). Lodewyckx (454) noted lymphocytosis in the spinal fluid principally in *B. duttonii* infections. The clinical picture appears to be dominated by the consequences of the hemodynamic changes in the C.N.S., their localization, and extent.

The heart may show endocarditis (607). Other authors (17, 391) have emphasized myocardial changes seen at autopsy. Hemorrhages of various size may be found in practically every organ.

Borreliae in the skin and the histology of the hemorrhages were studied by Taft and Pike (674) who found the organisms in the skin also between attacks, and by Judge and Perine (391) who investigated biopsy specimens.

Abortion is very frequent. About 92% of pregnant women lose their children when they contract relapsing fever (552).

It is expected that the variations of the borreliae, their particular predilection for certain localizations, the uncommon immunologic responses, together with the hemodynamic changes analyzed by Parry *et al.* (562) may assist in understanding the motley and protean clinical course of relapsing fever.

CLINICAL PICTURE

Attempts have been made to demonstrate a common denominator or to establish differential diagnostic criteria between louse-borne and tick-borne relapsing fever. Since we are confronted with one or more agents of varied pathogenicity and organotropy, with changes in the course of the illness according to epidemics and localities as well as with sick people but not diseases *per se*, this task is rather difficult if not impossible.

Clinical Course

The clinical course of relapsing fever has been described by several authors, such as Calwell (139), Selwyn-Clarke *et al.* (636), Robertson (606), Robinson (608), Davidson (215), Banwell and Kibukamusoka (67), Whitmore (731, 732), Bryceson *et al.* (127), and others to whom frequent reference will be made in this chapter.

Generally speaking, the course of human relapsing fever consists of an incubation period, the first attack, and, at intervals, of relapses. The typical "relapse course" is not always followed. There may be an irregular temperature curve (149, 345) or only one febrile attack (657). The severity of the disease often depends on circumstances which deserve further discussion even though the currently used classification (443) into severe, mild, ambulant, latent, and atypical forms, is of considerable use for recording.

Severity of the Disease

Tick-borne relapsing fever is usually more severe and more prolonged than the louse-borne type (149). There is an amazing variability, however, from outbreak to outbreak, as well as from one area to another. Individual susceptibility and residual immunity also may be important. While, for instance, in North and in East Africa *Borrelia* infections are severe in Europeans and mild in the local population (467, 642), in West Africa relapsing fever is equally severe in both Europeans and Africans. Variations in the severity of the disease according to geography are also interesting. Louse-borne relapsing fever was very severe in 1912 in Indochina (495) and in Gurkha laborers in Darjeeling (392), but it was very mild in Turkey and Egypt (139). Tick-borne infections have been de-

scribed as severe in Central Africa (685) and in Syria and Lebanon (624), mild in Israel (420) and West Pakistan (114), very mild in the Asian U.S.S.R. (655), but they show a wide variety of intensity in the Americas (443, 464). The severity of the disease seems to decline with the duration of the epidemic type caused by *B. recurrentis*.

B. hispanica infections are usually mild, as are those due to the crocidurae subgroup. This differs from the frequently severe *B. persica* infections. In the Americas, *B. hermsii* has been causing severe illness, *B. turicatae* usually mild disease, and *B. venezolensis* sickness of variable intensity.

Symptoms of relapsing fever, as shown above, vary with the immunity of the host, the strain of *Borrelia* that is involved, the phase of the epidemic, and a number of other less known or unknown factors. There are indications also that relapsing fever may exist with few or no clinical manifestations, particularly in endemic areas.

It is questionable from the clinical point of view if the "one day fever" often caused by *B. latyschewii* should be called relapsing fever *sensu stricto*.

Incubation Period

The incubation period was established partly by studying patients with general paresis who had been infected with *Borrelia* for therapeutic purposes, partly by epidemiologic observations, and, to a lesser extent, by experiments on volunteers.

In louse-borne relapsing fever the incubation time is 2 to 15 days, usually 5 to 8 days (176, 467, 503, 620). In Abyssinia, the incubation time is 4 to 14 days (127). Exceptions have been reported. One of these was that of two boys from Romania who became ill in Liverpool after having left their country 17 days previously, and were free from lice (542). Infection through the conjunctiva has produced disease in 8 days (429).

The incubation period of tick-borne relapsing fever in Asia and Africa could be established in several instances by determining the time that had elapsed since the individual visited a cave, a hut, or some other area where the tick vectors dwell. Geigy (303) observed it for 2 to 10 days in *O. moubata* infections. The incubation period in military operations in Tobruk (201) and in Cyprus (739) was

approximately 9 days. In Palestine and Israel (6, 253) it was 5 to 9 days, usually 7 to 8; in Tashkent (398) 6 to 14 days; in the Caucasus (475) 6 to 10 days; and in Mozambique (469) it was 5 to 14 days. *B. graingeri* caused clinical symptoms after 10 days (345). A very short incubation period was observed in North Africa (476), 2 to 4 days, while after infections with organisms of the crocidurae group (53), and from South Africa, periods of 4 to 12 days have been reported (469, 557).

Baltazard *et al.* (63) stated that the incubation period may depend on the number of borreliae that have penetrated into the body.

Observations of the incubation period made by feeding infected ticks on human volunteers had these results: López Portillo (460) used *B. turicatae* and found an incubation time of 3 to 7 days when the organisms were administered subcutaneously, and about 6 days when the infection was transmitted by the bite of *O. turicata*. Brumpt and Brumpt (124) observed a somewhat wider variation in the incubation period of *B. turicatae* infections: 4 to 19 days. Wheeler (727) fed infected *O. hermsi* on prisoner volunteers and established the incubation period as being 7 days. He himself became infected when the blood of an infected squirrel squirted on him. The incubation time was also 7 days. Thus, the incubation period in artificially infected individuals varied from 3 to 19 days, with a median of 6 or 7 days.

Wynns (740) estimated that the incubation period of relapsing fever in patients with the tick-borne variety in the United States is 7 to 14 days. The shortest period was 2 days, the longest 29. The same average incubation time was observed in Venezuela (573) and Ecuador (443). This period is somewhat longer than that observed in artificial infections and may be due to improper recall by some patients concerning the time of the tick bite, to differences in the various *Borrelia* strains, or to the number of borreliae carried by the individual ticks. Nevertheless, it seems that the average incubation time is between 5 and 9 days. However, especially in tick-borne infections, cases may also appear later, as long as 2 weeks and sometimes 3 weeks after exposure.

The First Attack

Some authors (557, 731) have reported prodromal symptoms such as headache lasting a few days, weakness, malaise, vertigo,

undefined aches and pains, perhaps also vomiting. Prodromes are seldom observed in the Americas (460, 464).

The onset is usually sudden. This was seen in China in 91.5% of the patients in louse-borne (176) as well as in tick-borne infections (93). The same observation has also been registered in other outbreaks and isolated instances.

The onset is usually accompanied by chills. This was observed in 90% of the patients in Villa Nador (503). During the attack, the body temperature usually ranges from 38.7 to 40° C (102° to 104° F), sometimes even 41° C (106° F) (429, 553). The fever lasts 3 to 13 days, on the average 4 to 7 days (282) or 5 to 7 days (388, 664) in the louse-borne form; 3 to 5 days in tick-borne disease (303, 464, 475, 739). Sometimes the temperature reaches its maximum in 24 hours, ascending more slowly. The fever is most often continuous with slight variations. The daily fluctuations, however, may be as much as 3° C (5.5° F). Sometimes, as in the Moroccan louse-borne epidemic (503) and in East and West Africa (467), a precritical rise in the temperature to 41° C (106° F) or less accompanied by profuse sweating, shivering, and even collapse may be observed. The attack ends with a crisis which will be discussed separately. The crisis lasts 1 to 2 hours, or somewhat longer. If the attack ends with a lysis, the course is 1 to 3 days. A typical fever course was seen in China in 96.8% of the patients observed by Jouveau-Dubreuhil (387) but this has been an infrequent finding in other instances.

The pulse rate is usually 110 to 120/min. However, it may show a broader range and wider variations (476). Except in the so-called "bilious" form, the pulse rate is comparable to the body temperature.

Violent occipital or occipito-frontal headache is the leading complaint. It is probably due to increased intracranial pressure. This symptom was emphasized in the World War II epidemic (298), in 90% of the patients with tick-borne infections in Iran (740), and in the louse-borne Abadan outbreak (87). Similar observations were made in 76.2% of the patients in North China by Chung and Chang (176), and others. Headache was not marked, however, in the Qetta episode (114).

Pain and tenderness of the muscles, especially the calves, are considered typical of the disease (205). Others (303) noted pain in

the neck. Backache was the principal complaint in 77% of the patients in Iran (87). Sometimes it radiates into the limbs. General aches were reported in 58.5% of the patients in North China (176).

A macular eruption is often seen, consisting of rose-colored spots spreading from the neck to the shoulders, then to the sides of the thorax, to the inner aspects of the thighs and the arms. This rash usually appears at the end of the first paroxysm. The spots may last 1 or 2 days or only a few hours (303, 551). In Abyssinia, it is rather common and either covers most of the skin or remains localized (608). Bryceson *et al.* (127) observed it in 17% of their patients. The rash was rare in Abadan (87) and absent in Qetta (114). In the Asian U.S.S.R. (551) a rash was seen only in 15% of the patients. It appeared shortly before the crisis of the first attack. In Texas, the eruption was described in about 50% of the patients, in other parts of the United States in about 4% (464). The eruption becomes petechial in severe cases. It was often hemorrhagic in Mozambique (469). In North China, a petechial rash was seen in 34.7% of the patients (176), while during the louse-borne outbreak in Morocco it was recorded in about 25%, according to Moreno Berdugo and Infante Gómez (503), who noted that petechial hemorrhages were rather common during the entire World War II louse-borne epidemic but appeared only shortly before the crisis in the World War I (551) outbreak.

Of other hemorrhagic phenomena, hematuria is rare but epistaxis has often been seen in North China, South Africa, and Peru (164). It is more frequent at the end of the first attack (557). Metrorrhagia and melena have also been reported but seem to be rare.

The gastrointestinal tract is frequently involved. Nausea and vomiting are usually present in about one-half of the cases in louse-borne epidemics (176, 620) and often in *B. duttonii* infections (303). The complaints may persist into the apyrexial period (647). They often appear only during the first attack (475) or only during relapses (557), or they may be entirely absent (6). Violent epigastric pain was reported in the louse-borne outbreak in Eritrea by Lanzo and Tresca (432) who called this complex of symptoms "pseudodysentery." These symptoms, as well as many others, depend on vasomotor disturbances and their sequelae and may vary from one instance to another.

Diarrhea may appear during the crisis (647) but it seems to be restricted to certain epidemics. It was rare in louse-borne relapsing fever in Spain, but frequent in Venezuela (573), and present in 14% of the patients in Northern China (175). Diarrhea might be the result of a secondary infection, as in Korea (17).

Constipation has been recorded in borreliosis (154). In North China, as many as 47.4% of the patients with this infection suffered from constipation. It is not known what treatment, if any, could have caused this condition.

The liver may or may not be enlarged. Bryceson *et al.* (127) found it enlarged or tender in 63% of the patients in Addis Ababa. Mild cases seldom show appreciable liver enlargement but this is a frequent finding in severe outbreaks (176, 464). Hepatomegaly was observed in 18% of the patients with *B. hispanica* infections (476). Others (93, 303) also emphasized painful liver. In South Africa, where the number of relapses is usually high in tick-borne relapsing fever, the liver becomes enlarged during relapses (557) and jaundice may also develop. Others, however, seldom observed enlarged liver in moderate or mild cases (114, 432, 460). Thus it appears that the liver is enlarged in serious cases or after several relapses.

Jaundice is frequent in relapsing fever in Abyssinia and accompanies pressure-sensitive liver also in Dakar (97). It was recorded in 29.4% of the patients in North China. A slight jaundice is often observed in African cases (71, 149). The time of onset of the icterus varies. It frequently appears on the third day of the attack, if it develops at all (573). While icterus does not point to a bad prognosis in patients in Peru and Cyprus (242), it is a serious indicator in Iran, China, and East Africa. The "bilious typhoid" of the old literature seems to be relapsing fever with liver involvement (731, 732). Icterus is difficult to see in dark-skinned persons. There may be only an icteric tint of the sclerae. Bryceson *et al.* (127) observed jaundice in 34% of their patients with the louse-borne form, di Benedetto (74) in nearly all cases in East Africa.

The spleen may be enlarged and tender (647) but it becomes smaller between attacks. Splenomegaly has been found in 34.7% of the patients in North China (176), in 10% in Eritrea (432), in 50% in both *B. recurrentis* (127) and *B. hispanica* infections

(467), in 33% of the cases in Texas (464), in 18% but only as a transient phenomenon in Mozambique (469), in nearly all instances in South Africa (557), and irregularly in other areas. Splenomegaly has seldom been seen in relapsing fever in the U.S.S.R. It was absent in Morocco (503) and in other parts of North Africa (467) except when complications such as malaria were simultaneously present. Splenic infarcts were found in 2.5% of the patients, mostly in males, even as early as during the first attack, in Egypt (595).

The size of the spleen, therefore, is not pathognomonic in relapsing fever.

Urinary tract involvements, such as nephritis, have been reported in Tobruk (201) and other areas, but the evidence that these were the result of relapsing fever is not satisfactory. Oliguria was observed in 25.2% of the patients in North China (176). Albuminuria has been found in the majority of the patients in East Africa (74) but rarely in the southern parts of Africa and in North America (see chapter on Pathology).

Respiratory symptoms are frequently observed in relapsing fever (156) also in the United States. Bronchitis and bronchopneumonia have been reported in 60% of the patients in Abadan (87) but only in 16.6% in Egypt by Omar (552). Respiratory symptoms are rare in Eritrea and Israel. Saddle-back temperature curves have been observed when bronchitis has developed during a relapsing fever attack (557). Cough was recorded in about one-half of the patients in Abyssinia but seldom in *B. duttonii* infections (590).

Respiratory symptoms are so frequent in some relapsing fever epidemics that they are often considered part and parcel of the disease proper rather than complications. Cough may be due, however, to hemodynamic changes in the lungs and to secondary infections (127).

Neuropsychiatric symptoms are more common in tick-borne disease than in the louse-borne epidemics. Nevertheless, Bryceson *et al.* (127) recorded meningeal symptoms in 30% of *B. recurrentis* infections. Insomnia is the rule. Tactile and taste hyperesthesias have been recorded by Simmons (647). Meningeal and central nervous system hemorrhages have been reported. Hemiplegias and aphasia have been observed, supposedly resulting from transient nerve defects caused by increased intracranial pressure or bleeding. Men-

ingeal symptoms are not infrequent in the United States (183) and in Spain (390). The spinal fluid contains an increased number of lymphocytes and its pressure is elevated (454). Pre-existing thiamine deficiency may be a predisposing factor for neuritis. On the other hand, the development of "wet" beri-beri has been observed after relapsing fever (180). Post-infectious neuritis may be ascribed to B-vitamin deficiency, principally in borderline nutritional states.

A fatal meningeal form has been described in Ecuador (443). In Africa, either gross central nervous system disturbances, such as aphasia and hemiplegia, are seen, or there may be involvement of specific nerves. Facial paralysis, sometimes of permanent nature, has been described (335). The neurotropic manifestations are transient and usually disappear in about 6 weeks (517). After about the same period after onset in *B. hispanica* infections, 3% of the patients developed paresis, but this cleared up in 3 to 4 weeks (620). Transverse myelitis is seldom seen. Epileptiform seizures have been reported (469), sometimes appearing simultaneously with neuralgia and neuritis.

If permanent paralysis develops, it is mostly that of the facial nerve (635). Encephalitic damage in relapsing fever has a tendency to remain stationary.

Psychoneurotic symptoms are frequent in patients in Syria and Lebanon (625), Kenya (296), Central Africa (454), Madagascar (517), North Africa (31), South Africa (633), and Poland (453), but they are less common in Dakar (93) and Abyssinia (156). They are rare in the United States. They may appear late, 2 to 2½ months after the onset of the disease, as in *B. duttonii* infections (582, 583).

Psychotic phenomena have been classified by Aubin *et al.* (31) as:

(a) Confusional, with terrifying dreams and possible suicidal tendency. This form is quite common.

(b) Anxiety complex, which may develop after a period of confusion. It is often maniacal, rarely depressive, with delusions, irritability, and impulsiveness.

(c) Protracted type, which is rare. Various hallucinatory and delusional forms were noted in this group.

The time of the appearance of psychotic disturbances varies.

They may be noted as early as during the incubation period. When they develop in convalescence, the symptoms tend to be atypical. The history of such patients often shows alcoholism and syphilis in addition to relapsing fever.

Ocular disturbances such as iritis, cyclitis, and chorioiditis have

TABLE 3
SUMMARY OF THE COURSE OF RELAPSING FEVER

	Louse-borne	*Tick-borne*					
		U.S.A.	*So. Amer.*	*Africa@*	*Mediterran*	*Near East*	*Central Asia*
Incubation period	5-8° (2-15)°	6-7 (2-14, s 14-20)	6-7	2-10 (2-14)	5-9 (4-11)	6-14 (5-18)	6-12 (5-14)
Duration of 1st attack	5-7 (3-13)	3-4 (1-19)	5-9 (1-20)	3-6 (1-10)	2-4 (1-5)	2-6 (1-8)	2-4 (1-6)
First afebrile interval	5-7 (3-9, s m)	3-14 (3-20)	4-15 (4-23)	6-8 (5-14)	7-15 (3-30)	irreg.	irreg.
Duration of subsequent relapsesx	1-4 (1-8)	1-3 (1-5)	1-3 (1-6)	5-6 (4-10)	1-5 (1-10)	irreg.	irreg.
No. of relapses	0-4 (0-10)	0-3 (0-5)	1-5 (3-8)	3-9 (3-20)	1-5 (1-18)	irreg. (0-10)	irreg. (0-20)
Course of disease	V	us. mild	us. moder.	oft. severe	V, oft. mild	oft. severe	V, us. moder.
Rash	+	++	+++	oft. hemorrh.	+	+	+
Icterus	++	V	++	+++	+	+	+
Hepatomegaly	+++	+++	+++	++++	++	++	+
Splenomegaly	+++	++	++	++++	++	+	±
Meningism	+	++	+++	+++	++	++	+
Severe C.N.S. involvement	+	+	++	+++	±	++	±
Extensive hemorrhages	+	±	+	++♯	±	±	±

@ East, West and So. Africa
° usual length, in days
° range, in days
s seldom
m more
x if any
V variable
♯ mostly in So. Africa

± in less than 10% of the patients
+ in 10 to 25% of the patients
++ in 25 to 40% of the patients
+++ in 40 to 80% of the patients
++++ in more than 80% of the patients

often been described (335, 469); these have a good prognosis. Conjunctivitis is common in South America and South Africa. Iridocyclitis is an important manifestation, having been observed in 3% of patients with *B. hispanica* infections. It persists for 2 to 3 weeks (476). It has also been observed in about 14% of the patients in East Africa. It is rare in the United States but frequently described in Madagascar (517). Hamilton (335) did not see ophthalmic lesions in Syria, but these were present in about 20% of his patients in the Western Desert of Africa. Both acute and chronic iridocyclitis were observed. The iridocyclitis may lead to synechiae which are easily broken down by mydriatics. This author (335) did not see chorioiditis but observed a gross vitreous exudate. The affection was unilateral and the prognosis for the vision was good. Chorioiditis was encountered, however, in both Cyprus (738) and Mozambique (469). Ophthalmia due to treatment with arsenicals was common during the World War II epidemic (298).

In Romania (205), middle ear infections ascending from the nasopharynx were reported in 70% of the patients. This complication is rare at present.

Different hematologic pictures have been reported from various areas. These have been discussed in the chapter on Pathology. Here we would like to record that Whitmore (731) noted a progressive anemia with a decrease in the red blood cell count and hemoglobin. This was seen also in louse-borne disease in Morocco, Spain, and China (388), and in tick-borne relapsing fever in Madagascar (672). In Madagascar, polychromasia and some poikilocytosis were also noted. A hemolytic tendency with the appearance of young red blood cells in the peripheral blood has been recorded in East Africa (67). Little hematologic response has been manifest either along the Mediterranean, in the U.S.S.R., or in the United States.

The platelet count is low (127).

The total number of white blood cells increases to 15,000 to 26,000 according to Simmons (647), but Whitmore (731) reported only a moderate leukocytosis. Variable counts have been reported by Beeson (71), from Israel (419), from the U.S.S.R., and the Western Mediterranean (503). A substantial leukocytosis

was considered a bad prognostic sign in China (163). Leukocytosis is frequently noted during bronchitis and when the fever rises.

The white cell count may be normal or elevated during the attacks as well as in the afebrile periods. This was seen in World War I (482), and was probably due to secondary infections. The number of leukocytes may be high during the attacks but it is low during remissions. A shift of the neutrophiles to the left is usually observed, especially while *Borrelia* persists in the body (482).

TABLE 4
SUMMARY OF CLINICAL PATHOLOGIC FINDINGS DURING FEBRILE PERIODS

Hemoglobin	very often decreased, principally during relapses
Red blood cells	frequently decreased
White blood cells	frequently increased but decreased before crisis in louse-borne, variable in tick-borne. if elevated during afebrile periods, sign of secondary infection
Shift to the left	very frequent, persists when attack will be repeated and in secondary infections
Eosinopenia	very frequent, except in helminthic infections
Lymphocytosis	frequent during attack, principally before crisis but often variable
Monocytosis	very frequent, may decrease just before febrile episode
Blood platelets	very frequently decreased
Red blood cell sedimentation rate	very frequently increased
Prothrombin time	frequently prolonged
Bleeding time	rarely prolonged
Clotting time	very frequently prolonged
Blood urea N	frequently increased
Plasma Cl	frequently decreased
Serum bilirubin	less frequently increased
Serum transaminases	frequently increased
Serum alkaline phosphatase	frequently increased
Total serum protein	sometimes increased
Serum gamma globulins	very frequently increased
Urinary protein	very frequently present, less often in the U.S.A.
Urine bile pigments	very frequently increased
Red blood cells in urine	frequently increased, very frequently increased in Africa

There is a decrease in the eosinophil count (234, 621). This may be the only abnormality in the blood picture (437). The number of eosinophils may be low only during attacks, especially if eosinophilia caused by parasites is present during afebrile periods (387). The number of lymphocytes may be increased during the attacks, especially during the crisis according to most observers, but it may fluctuate.

Monocytosis was the only change in the blood picture observed in Qetta (114). The monocyte count was increased during the World War I epidemic. In the region of the Chad in Africa, monocytes comprised as much as 60% of the white blood cells in the World War II epidemic (439). The number often increases in tick-borne disease (590).

The monocyte count often decreases before the onset of symptoms and increases during the relapse, reaching its maximum just at the beginning of the interval between relapses.

The sedimentation rate of the red blood cells is increased (744). Prothrombin deficiency has been noted in louse-borne relapsing fever in patients in Addis Ababa (127, 608).

The blood picture changes with the phases of the disease and, perhaps, also with the infectious agent.

Cardiac difficulties are seldom encountered in the United States. The electrocardiogram (ECG) has been normal in the examined cases (404). Abnormal ECG has been observed in louse-borne borreliosis (127), particularly a prolonged Q-Tc interval. Cardiac murmurs indicative of valvular endocarditis have been reported (607). Endocarditis and myocarditis, confirmed at autopsy, have been related by several authors (296, 475, 557 and others).

There usually is tachycardia during the attack, with a pulse rate of 100 to 140 per minute (460, 476). Tachypnea is the rule, with 28 to 42 respirations per minute.

Other symptoms are congested, but dry, face (476); furred tongue with red edges and a brown coating similar to that seen in typhus; and frequently abdominal pain and tenderness. Lymph node enlargement has also been noted at times.

It is often difficult or impossible to find the place of the tick bite on the skin of the patient. Louse-infested patients usually show many traces of insect bites.

Duration of the First Attack

As stated above, the initial attack in the louse-borne type lasts 3 to 13 days, on the average 4 to 7 days, according to the epidemic (453). In Abyssinia, it now lasts 4 to 10 days (127). In the Darjeeling outbreak (392), the first attack terminated after 8 to 10 days and there were no relapses. Such irregularities have been observed also in later epidemics (732).

The duration of the initial attack in tick-borne relapsing fever was recorded as 3 hours to 4 days in Palestine (6), as one day, seldom 3 to 4 days in the U.S.S.R. (398, 655), 2 to 4 days in Africa (557), and 9 hours to 9 days (usually 3 days) in the United States (464). Considerable variations were observed in *B. persica* infections (739). Thus the duration of the first attack of tick-borne relapsing fever is usually shorter than that of louse-borne borreliosis.

The Crisis

Crisis follows the partial or total disintegration of the borreliae in the circulation. There is a sudden, abrupt drop in the temperature, often to subnormal, accompanied by low blood pressure, intensive sweating, and weakness. The patient may go into shock. Convulsions due to cerebral edema or thrombosis, and myocardial failure may set in.

After the crisis, many patients feel weak. The further course of the disease depends on several factors, among which are the causative agent, the resistance of the host, and a number of unknown elements often designated as the *"genius epidemicus"*.

The Interval

There may be only one attack. In other instances, the body temperature, pulse rate, and blood pressure may remain subnormal or the patient may have no complaints or clinical symptoms until the relapse occurs.

The interval between the first attack and the subsequent first relapse varies. In louse-borne relapsing fever it may be 5 to 9 (664), usually 5 to 6 days (127). It was 3 to 16 days (176) in China, and 7 days (298) during the World War II epidemic. In tick-borne borreliosis this interval is irregular but usually lasts

one week (303), 4 to 15 days in South America, is irregular in Iran, and lasts 3 to 36 days in the United States (464).

Relapses

As a general rule, in louse-borne fever the relapses occur at shorter intervals than in the tick-borne disease (215, 647), but not in South America (460 and others). Relapses have a tendency to become shorter and milder as the disease gradually abates.

There is considerable variation, however, in the course of the illness, especially in epidemics. In Africa (298, 323), Europe (297 and others), and in China before World War I and during the World War II outbreak, only one relapse was observed in the majority of patients with louse-borne relapsing fever. About 5% had more than two relapses, with a maximum of 5. Relapses were more frequent in North China. In Abyssinia, up to 4 relapses are often seen (127). The interval between the relapses averaged 7 days in China, with a minimum of 3 and a maximum of 16 days. The duration of the relapses was 2 to 10 days, averaging 5 days. The time interval between the relapses was 7½ to 11 days in the Abadan outbreak, each relapse lasting 2½ to 5 days (87).

Relapsing fever carried by ticks usually shows many relapses, especially in Asia and in Africa. There are significant individual variations, however, (123, 739), which make the prediction of the course of an individual case difficult. Three to 5 relapses should be expected on the average. Their number may be more in Central Asia, up to 20 (398, 655). In Central Africa, usually 5 to 12 relapses, each lasting 5 to 6 days, occur (303). In the Americas, the patients fall in equal percentages into each of the following categories: no relapse, 1 relapse, 2 relapses, 3 relapses, and more than 3 relapses. *B. turicatae* infections, as well as borreliae of the crocidurae subgroup, cause few or no relapses. Three to 5 relapses, each lasting less than 3 days, have been described (60). The interval between the initial attack and the first relapse varies from 3 to 40 days, and the duration of the first and subsequent relapses from a few hours to not more than 4 days.

Thus louse-borne relapsing fever is usually milder than tick-borne, with short and few (1 or 2, maximum 6) relapses. The tick-borne variety is more severe and prolonged. The number of

relapses during this form of the disease generally varies from 2 to 5 in America and the Mediterranean area; in some infections in Central Asia and Central Africa as many as 10 to 22 relapses are often observed (303, 685, 731).

The total course of the untreated louse-borne relapsing fever is short, 1 to 2 weeks. Untreated tick-borne disease may last 3 weeks to 7 months (625).

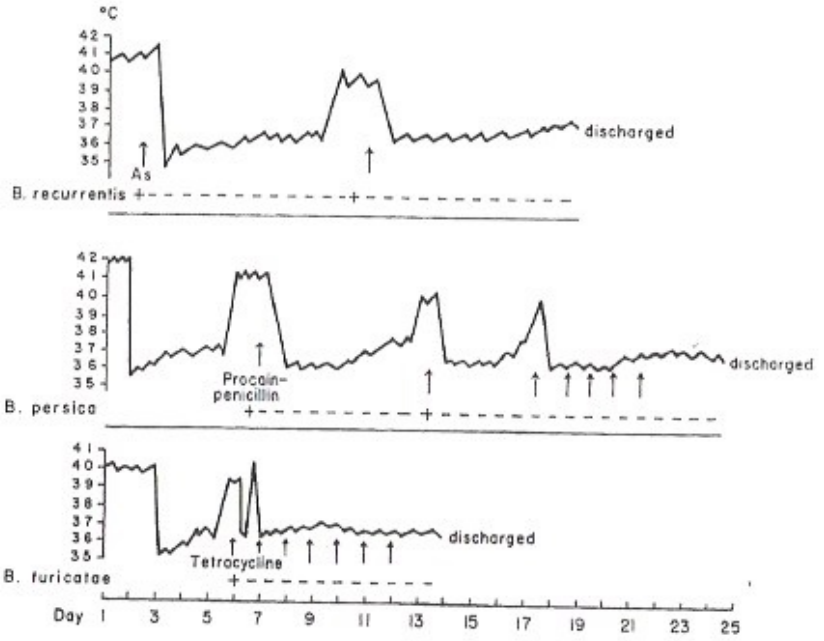

FIGURE 30. Fever curves of patients infected with various *Borrelia* strains.

Illustrative Case Histories

1. This patient was seen in China in 1933.

W.C.-L., a slightly built Chinese housekeeper, 52-year-old mother of 3 children, was brought to the hospital with complaints of fever and chills, nausea and vomiting, pain in the abdomen of indefinite location, and dry cough. The patient was apathetic, with a flushed face, and an icteric tint of the sclerae. The tongue was brown with clean edges. There were stridor and some rales audible at the base of the lungs. The liver extended about 6 to 7 cm below the costal margin in the parasternal line, and was sensitive on pal-

pation. The abdomen was tender over the colon and also around the umbilicus. The spleen did not appear enlarged on physical examination. The temperature was 40.8° C, the pulse rate 110 per minute, the blood pressure 110/65 mm Hg. There was lethargy, some nuchal rigidity, diminished abdominal reflexes, and pain in the limbs on palpation.

Blood, spinal fluid, urine, and stools were collected for laboratory tests.

The next day the sensorium remained unchanged. Vomiting ceased. The sclerae were suffused and remained icteric. The rales persisted over the lungs. The patient complained of backache and pain in the legs. The liver was more tender than on the previous day but its margin did not appear altered. The spleen was soft and tender. Nuchal rigidity persisted. The temperature remained elevated.

The laboratory reported increased urobilinogen in the urine, no sugar, 2+ protein, a positive benzidine reaction, few hyaline casts, but only rare red blood cells. Total serum protein was 8 Gm%, blood urea 55 mg%, and blood sugar 87 mg%. The icterus index was 14. The spinal fluid showed 15 cells per cu.mm, 42 mg% glucose, 68 mg% protein. Hematologic examination revealed 3.9 million red blood cells, 11,000 white blood cells, 9.9 Gm% hemoglobin, and a differential white cell count of 18% juveniles, 30% segmented neutrophils, less than 1% eosinophils and basophils, 13% monocytes, and 39% lymphocytes. The erythrocytic sedimentation rate was 105 mm per hour.

Agglutination tests with *Proteus OX19, OXK,* and typhoid antigen were negative. Malarial parasites were not found in the blood films but borreliae were present. A diagnosis was therefore made of borreliosis, or relapsing fever.

The patient was given 40 mg Mapharsen intravenously, and 15 mg codein t.i.d., the latter to alleviate the pain.

The next day the temperature fell abruptly to 34.8° C. The pulse rate was 100 per minute. The blood pressure dropped to 70/40 mm Hg. The patient was drenched with sweat. Petechial hemorrhages appeared over the trunk and upper limbs. According to the practice prevailing at that time, adrenalin was administered.

During the subsequent 6 days, the patient appeared very weak.

The hemorrhagic spots disappeared progressively. Lack of appetite, and some pain in the lower limbs persisted. Nuchal rigidity was not apparent, and the deep muscular reflexes were normal. The liver and spleen returned to approximately normal size. Borreliae were not found in the blood that was examined daily. On the seventh day after the first attack, the patient suddenly developed chills, the temperature rose to 39.8° C, the eyes became bloodshot, the face flushed and dry. Borreliae reappeared in the blood stream. There was some hesitation to repeat the administration of the arsenical because it was not certain whether the hemorrhagic phenomena were due to the usual course of the disease or were part of a reaction to Mapharsen. The fever continued, splenic enlargement became more accentuated, and signs of meningeal irritation developed, including a positive Kernig's phenomenon. Mapharsen was therefore repeated, 30 mg intravenously. This was followed by an abrupt fall in the temperature. The pulse rate was 80 per minute. The sweating was profuse but there were no hemorrhagic phenomena. The liver did not become enlarged. The blood picture showed 8,000 white blood cells, 3.5 million red blood cells, 8.9 Gm% hemoglobin. Recovery was uneventful, except for a feeling of weakness. Borreliae were not seen again in the blood films. The patient was discharged 7 days later.

The causative organism was classified as *Borrelia recurrentis* in cross-protection tests in mice against the Chinese type strain.

The patient appeared to be in an adequate physical condition before discharge. The spinal fluid protein was 12 mg%, glucose 42 mg%, the cell count 3 per cu.mm. The urine did not show increased urobilinogen, and tests for protein and sugar were negative. There were a few hyaline casts and leukocytes in the sediment. The blood urea was 20 mg%; the serum icterus index 4. There were 6,000 white blood cells per cu.mm. The differential count was juveniles 6%, polymorphonuclear neutrophils 60%, eosinophils and basophils 2%, monocytes 8%, lymphocytes 24%. The red blood cell count was 3.3 million cells per cu.mm.; Hb 8.7 Gm%. Treatment with iron preparations was recommended, and the patient was transferred to the clinic.

2. This patient was seen in Afghanistan in 1948.

A.M.E.H., a well-built Afghan male sheepherder, 24 years old,

single, living with a group that had been moving with their livestock, and sleeping under tents or in caves.

He was admitted to the hospital with 42° C fever, pulse rate 140/min, flushed face, a few roseolae on the abdomen, and complaining of headache and pain in the back. The spleen was moderately enlarged and painful on palpation. There was no jaundice. The liver was within limits considered normal. There were conjunctivitis and photophobia. The abdomen was not tender, except for the left upper quadrant. Physical examination did not reveal other abnormalities. The urine analysis report was specific gravity 1.032; no sugar or casts, but protein was present. The blood films were negative for parasites. The tentative diagnosis was F.U.O. (fever of unknown origin), perhaps smallpox, and the patient was put into isolation.

The temperature suddenly decreased to 35.7° C the next day. The patient was sweating profusely. The pulse rate was 65 per minute. He was restless and complained more of thirst than of pain. Later after the abrupt fall in the temperature the patient felt well. Daily blood film examinations did not reveal parasites. Bacteriologic cultures of the stools were not indicative of a *Salmonella* infection. Blood cultures remained negative. On the fourth day after the crisis, the patient developed chills and high fever. The blood films revealed borreliae. A diagnosis was therefore made of relapsing fever. He was given 500,000 units of procaine penicillin intramuscularly. Shortly thereafter a crisis took place. It was believed that the patient was on the road of recovery, when 5 days later the temperature again reached 40.1° C. Procaine penicillin was repeated in the same dosage. The temperature dropped abruptly, and the patient remained symptomless for 3 days, when the temperature rose somewhat more slowly to 39.8° C, and borreliae again appeared in the blood. Thereafter procaine penicillin was repeated daily for 5 consecutive days, 500,000 units per day. The proteinuria disappeared at that time. There were no subjective complaints. The spleen became smaller and was no longer tender. The patient was discharged 6 days after the last relapse.

The meager laboratory studies of this case were due to the inadequate facilities available at the local hospital. The organisms were tested in the Pasteur Institute of Teheran and classified as *B. persica*.

It does not seem that penicillin in the doses administered was of much value in this case.

3. This patient was seen in Thailand in 1958.

A.S.B. was an American boy, 11 years old, somewhat overweight, who had returned with his parents from home-leave in Texas. There he had romped in the woods around their home until the day before the family returned by fast air transportation to Bangkok. A few days later he developed fever and chills, vomited several times, started coughing, and complained of severe headache and pain in the chest and in the limbs. On admission to the hospital, his face was dry and flushed, the conjunctivae were injected, and the muscles of the abdomen and the limbs were tender. The rest of the physical examination did not reveal any deviations from the normal. Chest x-rays and the results of urine examinations were negative. Tests on the serum showed 11 mg% Ca, 605 mg% Na as NaCl, 31 mg% urea, 8.1 Gm% protein (albumin: globulin ratio 1.3:1). Plasma fibrinogen was 170 mg%. The prothrombin time was 13 seconds, the coagulation time (glass tube method) 17 minutes, the hematocrit value 38 ml%. Hematologic studies revealed 12.8 Gm% hemoglobin, 4.6 million red blood cells, 120,000 platelets, and 5,000 white blood cells per cu.mm. There were 10% juvenile neutrophils, 24% segmented neutrophils, less than 1% eosinophils and basophils, 58% lymphocytes, and 18% monocytes. The tourniquet test showed 4 petechiae in a 5 cm circle after 5 minutes with the cuff at 100 mm Hg pressure. Blood, urine, and stool cultures were negative. No malarial parasites were found in the blood films.

The tentative diagnosis was fever of unknown origin, perhaps dengue fever. Blood specimens were submitted for virologic examination. The patient received aspirin which reduced the pain but did not influence the course of the fever. He was also given 5% glucose infusions with B-vitamin complex. On the third day the patient was apathetic, and a papular exanthem appeared on the flexor surfaces of the arms, spreading distally but disappearing after 6 to 7 hours. Then the patient started sweating, and the temperature fell from 40.4° C to 35.5° C within a few hours. The pulse rate decreased from 135 to 65 per minute, and the blood pressure dropped from 105/75 to 70/40 mm Hg. The patient felt better,

and the temperature as well as the blood pressure began to return to normal. Pains and aches appeared again on the third day after the crisis. Chills and fever returned, just at the time when young mice inoculated with the patient's blood collected during the first attack showed borreliae in their circulation. A thorough check of the blood films collected during the second episode also revealed these organisms. A diagnosis was made of relapsing fever.

Tetracycline was given, 0.1 Gm parenterally. An immediate critical drop in the temperature was observed followed by a brief rise to 40.3° C. The borreliae disappeared from the blood, and after drenching sweat for a few hours, the pains subsided and the patient appeared to become interested in his environment, responsive, thirsty, and hungry. It was decided, therefore, to maintain tetracycline medication at a low level for 6 more days, administering per os 0.25 Gm twice a day. Recovery was uneventful. The organisms were diagnosed as *B. turicatae* by immobilizine and borreliolysin tests using antisera against *B. turicatae, B. parkerii,* and *B. hermsii.*

At discharge, the patient had no complaints. Chest x-ray, E.C.G., urine, and spinal fluid examinations showed no deviations from the normal for his age. The blood serum showed 12 mg% Ca, 585 mg% Na as NaCl, 28 mg% urea, 6.5 Gm% protein (albumin: globulin ratio 1.4:1). Plasma fibrinogen was 240 mg%. The icterus index was 4. The prothrombin time was 12 seconds, the coagulation time 15 minutes, the hematocrit value 40 ml%. Hematologic studies revealed 12.3 Gm% hemoglobin, 4.2 millon red blood cells, 210,000 platelets, and 7,000 white blood cells per cu.mm. There were 3% juvenile neutrophils, 42% segmented neutrophils, 3% eosinophils, 1% basophils, 45% lymphocytes, and 6% monocytes. The tourniquet test showed no petechiae.

It was possible to obtain serum samples from this patient also after convalescence. There was an increase of the immobilizine titer from less than 5% in the sera collected during the attacks to 53% and 61%, respectively, one and three months after discharge from the hospital. The borreliocidin titers reached 1:360 at the same time. Cross-reactions with cardiolipin were not observed but a serum sample collected during the second attack gave an agglutinin titer of 1:40 with *Proteus OXK* but not with *Proteus OX19.*

The temperature curves of these patients are shown in Fig. 30.

Atypical Forms

The temperature curve may show aberrations. In tick-borne cases in Iran, variations have been recorded from mild fever for a few days without relapses to severe disease with irregular temperatures for 14 to 16 days, followed by irregular spiking remissions (739). Long paroxysms of continuous low-grade fever were also seen in the Mediterranean area.

Very mild, ambulatory but protracted tick-borne cases have been reported from the Southeastern Mediterranean (419, 420), contrasting with fulminating disease that killed the patient within 24 hours, in Africa (467).

Atypical forms have been grouped according to the predominant clinical syndromes by several authors, as in Abyssinia (240), in North Africa (395), and in Ecuador (443). These forms may be summarized as ambulatory, dysenteriform, typhoid-like, hepatic, biliary, pulmonary, meningoencephalitic, and rheumatoid.

Schuhardt (630) explained the different number of relapses by the diverse ability of the various *Borrelia* strains to form antigenic phase variants during the disease to which antibodies are not available as a result of immunologic experience acquired during the previous course of the disease. There is no explanation for the difference in the capability of various strains to form such phases. One may consider them an expression of the antigenic instability of borreliae, which supports the concept that there is only one species of *Borrelia,* and all *Borrelia* types we are speaking and writing about are mere variants of only one single microbial entity. Awareness of these atypical forms is important not only for the clinician but also for the epidemiologist, particularly in the beginning and at the end of epidemics when they appear more frequently.

Complications

Otitis, parotitis, and arthritis have been listed in standard textbooks. Cardiac disturbances frequently occur in the Caucasus, Kenya (296), Abyssinia (127, 608), and in Ecuador (443). In South Africa (557), heart failure and residual arthritis causing "rheumatic" pains have been observed. In addition to circulatory disturbances, hemorrhages, principally in the central nervous system, may cause problems.

Hepatic failure is a serious complication.

Splenic rupture may cause death. More than 90% of pregnant women abort when infected with *Borrelia* (298, 552).

Herpes labialis is frequent, especially in louse-borne infections (503) but may occur also in tick-borne borreliosis with varying frequency (335, 476, 503).

Secondary infections of the respiratory tract are common. Salmonellosis is often a fatal secondary infection (17). Epidemic typhus fever presents a grave menace (734). Latent malaria and kala azar may be activated by relapsing fever (202).

Reinfection

Kudicke *et al.* (427) called attention to the role played by treatment in the development of resistance against reinfection. If the disease has terminated abruptly, before antibodies developed, reinfection with the same strain appears a distinct possibility. Reinfection, however, is rare in louse-borne epidemics if proper hygienic measures are enforced, principally delousing and prevention of reinfestation with ectoparasites. However, reinfection may occur in 2 months according to Simmons (647), in 1½ to 6 months according to Whitmore (731), and in one year according to Más de Ayala (476). In tick-borne infections in Central Asia, Kassirsky (398) observed a shorter period of immunity against reinfections but Grothusen (326) demonstrated that the disease caused by *B. duttonii* in Africans may be as severe as in Europeans who did not have an opportunity to acquire premunition during their childhood. Childhood infection is, however, of paramount importance for the response to a later infection according to other authors (263, 303, 443, 715, 732).

Apparently, recurrence *versus* reinfection should be re-evaluated also in relapsing fever (263).

Hereditary immunity is a moot question. Nohira (546) demonstrated in rats that the offspring of the female infected with *B. recurrentis* is immune to the homologous strain for about 2 months. Women with relapsing fever usually abort and few data are available about infants delivered at term, except in studies of congenital transmission. Such instances were described in the United States (183, 283, 505); by Garnham (1936), Caldwell (1936), Kröber (1936) and Correa *et al.* (1964) in Africa (139, 203, 292, 424); and in other areas (176). Further studies of transplacental antibody transmission are most desirable, principally in regard to the recent concept of immunoglobulins of which only the small-sized IgG appears to be transmitted to the newborn.

Prognosis and Mortality

Sterling-Okunewski (669) demonstrated that the number of borreliae in the peripheral circulation has no bearing on the severity of the disease or on the prognosis of relapsing fever.

Mayer (482) considered continuous high fever, deep jaundice, extensive hemorrhages, and coma as bad prognostic signs. León and León (443) added to this list endocarditis and myocarditis. Bryceson *et al.* (127) called attention also to persistent Q-Tc interval changes in the ECG, disseminated intravascular coagulation. hepatic failure, cerebral edema, and shock as serious prognostic signs. Pneumonia was cause for a bad prognosis in China (176).

The disease frequently has a severe course in infants.

The case fatality rate in louse-borne relapsing fever depends on the nature of the epidemic and on the availability of treatment. The average mortality in Europe was 4 to 5%; however, in China, Indochina, and India before World War II it fluctuated between 25 and 80%, especially in untreated individuals (495, 731). The small but severe outbreaks in Darjeeling (392) and Assam (152) produced many fatalities, while in Iran few treated patients died (337). On the other hand, in Peru, in spite of the lack of intensive medical care, the case mortality rate was below 2% (164).

During World War II when arsenicals were routinely used, only 0.25% of the treated patients failed to recover, whereas in China about 40% of untreated patients died (163). In Abadan, where good medical care was available, the mortality rate was 1.1% (87). Wide variations, from 1 to 46%, were observed in Tunis, varying according to the locality and the available treatment (323).

In the epidemic following World War II, the case fatality rate was 5 to 10% in untreated individuals, 8.5% in the poor, and 3.6% in the well-to-do (298). The mortality rate among children reached 65% in some areas.

Manson and Thornton (467) calculated a case fatality rate of 0.3% in East Africa, and 4% in West Africa. Garnham *et al.* (296) encountered a 40% mortality among the untreated. Geigy (303) reported 0.7 to 70% deaths.

The mortality figures in crocidurae subgroup infections and in patients in Central Asia are low (398). In the Americas, few of the tick-borne infections cause death (137, 740) except in Venezuela where 27% of the patients died (18). Higher rates, up to 5%, have been reported from Africa (577).

The introduction of antibiotics in the treatment of relapsing fever has greatly reduced the mortality rate.

Laboratory Diagnosis

Microscopic examination

The laboratory diagnosis of infection with *Borrelia* is often made during the attack by examining thin and thick blood films. The slides are stained in Giemsa solution in water at pH 7.2 or with the Wright stain, followed by 10 or 30 seconds in a 1% solution of crystal violet.

Thin blood films should be fixed with acetone or methyl alcohol for 3 minutes before the Giemsa stain is used. Thick smears should be dehemoglobinized with 0.5% acetic acid, carefully washed with water at pH 7.2, and stained without fixation. The evaluation of thick smears may cause difficulties to the less experienced technician.

Laboratory workers often prefer to examine blood preparations under dark field illumination. A drop of the patient's blood is placed on a slide, covered with a coverslip, and the coverslip hermetically sealed with liquid paraffin, wax, a mounting medium, or nail polish. Borreliae remain alive; their movement can be observed with ease in such preparations for several hours.

Fluorescent microscopy requires special equipment and antisera (184). It is practical in areas where only few *Borrelia* serotypes have to be considered.

Borreliae may be sparse in the peripheral circulation during attacks, especially in children (139, 365). Borreliae are usually absent from the blood during the periods between relapses.

In tissues, they can be demonstrated by a silver stain, e.g., that of Krajian which is described in the Appendix.

Animal inoculation

The "standard" animals are young mice which are susceptible to all known human relapsing fever strains. They may or may not

succumb to the infection but the borreliae will circulate in their blood. Mouse inoculation is also feasible for examination of the C.S.F. The mouse test is considered superior to the examination of slides (90, 92, 338), whereas Gönnert and Mudrow-Reichenau (320) prefer microscopy to animal experimentations. Chohan (166) recently reemphasized that injecting mice with blood of patients gives better diagnostic results than examining blood films. He studied *O. tholozani*-borne relapsing fever in Kashmir. Only 15.2% of the blood films in clinically ill individuals revealed borreliae. The organisms did appear, however, in the blood stream of the mice 2 to 3 days after inoculation with the patients' blood, and remained in the circulation for 3 to 4 days. This author isolated borreliae from the patients blood with the aid of mouse inoculation also during the apyrexial period.

Usually, 6 to 8 young mice are inoculated intraperitoneally, each with 1 to 2 ml blood of the patient. Borrelemia appears in 2 to 3 days as a rule but it is good practice to examine the blood of the mice for a week before considering it negative. The blood is collected by clipping the end of the tail of the mouse and is examined by dark field illumination or after staining according to Wright or Giemsa.

When mice are inoculated with spinal fluid, 0.5 to 1 ml amounts may have to be injected, and the number of mice reduced if only insufficient amounts of C.S.F. are available.

Mice do not often have relapses. Young rats have also been used but borreliae sometimes suddenly disappear from their blood, even though relapses may be observed in them.

Xenodiagnosis

Baltazard *et al.* (51) applied xenodiagnosis, with good results.

The use of *O. moubata* was recently recommended for this purpose by Geigy (303). Five to 10 ticks are fed on the patient during the febrile period and specimens of the hemolymph are examined after a few weeks following aspiration with a capillary tube (129).

An absolute prerequisite for this test is that a tick colony free from borreliae and other infections and infestations be at hand.

Serologic Tests

Serologic tests are seldom helpful during the first days of the disease.

Schuhardt (630) and Felsenfeld (264) summarized the tests used in the serologic diagnosis of *Borrelia* infections, the difficulties due to phase variations of the infective strains in the patient, and the disadvantages inherent in such tests. Production of sufficient amounts of antigen is toilsome because the organisms cannot be easily grown in laboratory culture media.

Agglutination

The value of the agglutination tests is hampered by the natural tendency of the borreliae toward autoagglutination. Balteanu *et al.* (65) were able, however, to demonstrate rising agglutinin titers after attacks.

In our hands, the method of Turner for leptospirae (693) gave good results if adherence could be avoided. Organisms were isolated from rat blood after hemolysis with distilled water at pH 7.2, then centrifuged for 30 minutes at 6,000 r.p.m., and then treated with neutral formol to give a final concentration of 0.2%. The slide method was employed, using 0.01 ml of the antigen, and an equal volume of two-fold serum dilutions. The slides were sealed hermetically, incubated at 37° C for 2 hours, then examined at ×100 magnification by darkfield illumination. We do not recommend this procedure for routine use.

Adhesin Test

The adhesin test has been recommended by Brussin (125) and Schuhardt (360).

The adhesin tests is carried out by mixing serial serum dilutions, a suspension of borreliae, and an *Escherichia coli* suspension, incubating for 20 minutes at 30° C, and then reading the results by darkfield illumination. Adhesion of the borreliae to the *E. coli* organisms can be seen if the test is "positive." Schuhardt (630) observed that a particulate substance does not have to be added if defibrinated nonreactive blood is mixed with the examined serum and the *Borrelia* suspension.

The adhesin test is difficult to replicate and is, therefore, seldom carried out.

Complement Fixation

The complement fixation test was advocated by Toyoda (688).

Complement fixation gives low titers (up to 1:100) either with saponin-treated blood of infected rats (688) or with phenolized egg-grown antigen (737).

The technic of Wolstenhome and Gear (737) consists of inoculating developing chick embryos with mouse blood, harvesting the borreliae one week later after bleeding from the allantoic veins into the allantoic fluid, and passaging this embryonic blood-*Borrelia* mixture ten times through fertilized chicken eggs. The final harvest is taken up in 0.5% phenol-saline, centrifuged, and the supernate used as the antigen. At least 100 borreliae per oil immersion field are necessary for the preparation of a good antigen.

Considerable cross-reaction between the strains, and anticomplementary phenomena frequently mar this test.

Borreliolysin

Several authors (43, 65, 72, 136, 262, 572, 630 and others) have found the borreliolysin test valuable. For instance, Balteanu *et al.* (65) found titers up to 1:1,000 after attacks. Ballif *et al.* (43) stated that high borreliolysin levels may be found as early as during the crisis in *B. recurrentis* infections. Borreliolysin titers up to 1:20,000 have been observed. Pfister (572) reported excellent results employing this test in relapsing fevers caused by *B. hispanica*. Lysin-fast variants may develop, however (132), which do not react in this test.

The borreliolysin test may be carried out with fresh serum to which an equal amount of a standardized suspension of borreliae in physiologic saline is added. Schuhardt (630) recommended that serum and antigen be drawn into a small capillary tube, with a rubber bulb at one end. The contents of the capillary are expelled on an ordinary microscope slide or into a welled slide, mixed, then redrawn into the capillary. The capillary is sealed with wax or clay, incubated at 37° C for 2 hours, the sealed end is broken, and the contents are emptied onto a slide. The number of borreliae are counted under darkfield illumination and compared with the number of organisms in the control, which contains an equal amount of physiologic saline instead of serum.

Balteanu *et al.* (65) found that treatment of the patient may interfere with the test. The borreliolytic activity of the serum persists unchanged in refrigerated serum for 10 months. These authors also used dried blood samples for the test.

Borreliolysin is complement-dependent (265, 268). We, therefore, add guinea pig complement diluted 1:100. Diluting fluids

that are supplied with some commercially available desiccated complement contain a preservative, e.g., sodium azide, and cannot be used to reconstitute the dehydrated complement if it is to be employed in this test. The complement is diluted instead with 0.01 M phosphate buffer, containing 5 mM calcium chloride, pH 7.2.

Slides or microplates that fit under a microscope can be used for the test. Our standard *Borrelia* suspensions contain 20 to 30 organisms per high power field. An equal part of serum, inactivated at 56° C for 30 minutes, is mixed with live *Borrelia* suspension. After 30 minutes at 37° C, one part of the diluted complement is added. After 90 minutes further incubation at 37° C, the number of surviving borreliae are counted and compared with the controls. One control contains one part of the *Borrelia* suspension and two parts of physiologic saline, the other equal parts of physiologic saline, *Borrelia* suspension, and diluted complement.

Aliquots of 0.02, 0.025, or 0.05 ml of each component are used. Desiccation must be prevented during incubation. Keeping the slides in a "moist chamber" with a wet piece of filter paper on the bottom will serve this purpose.

The reaction may be carried out in tests tubes, using larger amounts of the reactants. Adequate samples are transferred from the tubes, with an automatic pipette, to slides for microscopic examination.

It is recommended that the borreliae be counted in at least 10 fields, and the results expressed in per cent of organisms lysed. For instance, if 300 organisms were counted in the control and 120 in the slide containing the examined serum, 180 borreliae were lysed, i.e., 60%, which is the titer of the serum.

Schuhardt (630) stated that *immobilizines* may or may not be related to lysins. Our group (264, 265, 268) reported that immobilizines are not complement-dependent. Several authors (449, 450, 598, 697) believed the test for immobilizines to be valuable. Alline and Marx (12) saw good results, principally after absorption of the sera with Reiter's spirochete. This considerably increased the specificity of the reaction. It is recommended that this principle be followed.

Immobilizine is tested for by mixing an equal amount of a live suspension of borreliae and absorbed serum according to the

technic used in the borreliolysin reaction but without complement, to establish the proportion of the borreliae that have lost their motility under the influence of the serum.

The reaction has not yet been standardized. The incubation time is different, 10 to 30 minutes, and the test may be carried out at 37° C but also at room temperature before the proportion of the immobilized borreliae is determined under darkfield illumination. The procedure used in some laboratories varies principally according to the *Borrelia* strain and the availability of the live borreliae. We prefer 10 minutes incubation at 37° C with American *Borrelia* strains for routine diagnostic tests.

Utmost care must be exercised in performing both tests, to avoid loss of material and changes in proportion of the reactants. Needless to say, only competent laboratory personnel should handle live borreliae.

Cross-reactions

Frequent cross-reactions in the Wassermann and Kahn tests and with *Borrelia* antigens may be due to the close relationship of borreliae and other Treponemataceae, to the related antibody, principally of that of the immunoglobulin designated IgM as well as the affinity of the antibody for cardiolipin as pointed out by Amiraian and Leikhim (14). Positive Wassermann reactions were encountered in relapsing fever by Chang (154) in 30% of the specimens from relapsing fever patients, and often by others (263, 296, 604). The test may be positive for a transient period only (745). Positive Kahn tests were reported in 15% of the examined relapsing fever sera in China (154), and in Cyprus, for a transient period (154, 242), in some instances of *B. duttonii* infections, but Garnham *et al.* (296) recorded only negative results with the Kahn test in their patients. Others (173, 512) also pointed out the occurrence of positive results in serologic tests for the diagnosis of syphilis in relapsing fever.

No explanation has yet been offered for the positive agglutination test results with *Proteus OX* strains in some instances of relapsing fever. This cross-reaction may present serious problems when both louse-borne typhus and relaping fever epidemics break out simultaneously.

The aggultinin titer with *Proteus OXK* was reported to be fre-

quently high in China (606), in Abyssinia (608), and in other parts of Africa (256). Positive tests with *Proteus OX19* as well as with *Proteus OXK* antigens have been recorded (395, 745). Rising *Proteus OX* agglutinin titers were observed during the course of relapsing fever, as well as positive complement fixation tests with *Rickettsia prowazeki* antigen (395).

Unfortunately, pre-infection sera are not available from patients showing such reactions. The collection of post-convalescent blood samples may also cause considerable difficulties. Further investigation of this problem is, therefore, also necessary within the huge problem-complex of borreliosis.

Differential Diagnosis

The principal differential diagnostic problem is malaria in regions where both diseases occur (11, 112). In addition to blood films and the inoculation of mice, clinical observation may be helpful. The heart and the peripheral circulation are usually little disturbed in malaria, but in relapsing fever low blood pressure and signs of cardiac failure may be impressive during the crisis. The liver is not usually painful in malaria, but it is often sensitive to pressure in relapsing fever. The headache in malaria is frontal but it is frequently occipital in relapsing fever (112). Sweating sets in early in malaria, late in relapsing fever (590).

When malaria and relapsing fever develop simultaneously in an individual, splenic enlargement and irregular fever are the outstanding symptoms (467).

Additional differential diagnostic problems are leptospirosis, plague, pneumonia, dengue fever, yellow fever, influenza, typhus, early and hemorrhagic smallpox, meningococcal infections, rat bite fever, and acute abdominal conditions, such as appendicitis, cholecystitis, peritonitis etc. because palpation and pressure often cause pain in various regions of the abdomen (690).

During World War II, the German Army on the Eastern Front was infected with louse-borne relapsing fever. Since neurologic symptoms often prevailed, the disease was mistakenly considered a new entity and named "febris neuralgica periodica" (101).

Numerous attempts have been made to differentiate louse-borne and tick-borne relapsing fever by clinical examination and

observation only (186, 187), but this is sometimes an impossible task without the aid of laboratory study of the organism involved, and up-to-date epidemiologic information.

Treatment

Anti-Borrelial Agents

Arsenicals have been used in the treatment of relapsing fever practically ever since their introduction in the therapy of syphilis. Pentavalent arsenicals have been superseded by antibiotics, principally because of fewer side effects (590), and their greater efficacy.

Several investigators (154, 298, 731, 734), however, reported favorable results with arsenicals in mass-treatment during epidemics but called attention to the rather frequent Jarisch-Herxheimer type reactions that occur during the application of highly effective arsenicals.

The drug of choice of this writer (O.F.) was oxophenarsine hydrochloride (2-amino 4-arsenophenol hydrochloride, Mapharsen, Mapharsal, Fontarsan), 30 to 60 mg intravenously, preferably administered during the interval between relapses, or when the fever was rising.

The Jarisch-Herxheimer response will be discussed later because it also follows other types of treatment.

Sulfonamides have been found ineffective (380).

Antibiotics have been tested extensively in animals. Such experiments were reviewed by Vetrogradova (704) and Ercoli *et al.* (258). Penicillin was found satisfactory in the laboratory in doses of 500 to 1,000 U per Kg in rats (210, 259, 330, 412).

Penicillin in doses of 1 million units prevented relapses in human louse-borne disease (378) and was considered a satisfactory drug (323, 674). It was emphasized (443) that at least 500,000 units must be administered. Penicillin failed to prevent relapses in tick-borne relapsing fever (303, 420, 517).

Combinations of streptomycin and penicillin were found effective in rats without brain involvement by Levaditi and Vaisman (447) but were considered of lesser value by Bijlmer (77). Streptomycin, 1 Gm per day alone, did not prevent relapses in man in the Kashmir (516), nor in *B. duttonii* infections (447).

No synergism between penicillin and arsenicals was observed

(147). Neither were penicillin and chloramphenicol combinations effective in rats infected with drug-resistant *B. duttonii*.

Chloramphenicol (Chloromycetin®) was considered ineffective in *B. duttonii* infections (303). Cambournac *et al.* (140), Hirschboeck (336), and Gimeno de Sande (317) observed that 1 to 2 Gm, divided over a period of one or two days, were curative but Jarisch-Herxheimer-type reactions were difficult to manage especially in children, if such consequences of the treatment developed. The blood dyscrasias that develop during the crisis or before it may play a role in these difficulties. Nevertheless, it appears that chloramphenicol deserves further trials in louse-borne relapsing fever in adults without neurologic symptoms and without severe hematological changes.

Chlortetracycline (Aureomycin®) gave good results in rats (7, 339) but did not prevent delayed brain invasion by borreliae (351, 366). In tick-borne relapsing fever, chlortetracycline, in doses of 2 Gm per day for 7 to 10 days, was effective in trials in Eritrea (432). Satisfactory results were recorded in tick-borne infections (140, 162).

Oxytetracycline (Terramycin®) cleared animals inoculated with *B. duttonii* (75). Success with this drug was reported also in man (140, 162, 352).

Tetracycline (Achromycin®) has become the drug of choice (127, 238, 553, 562, 629). It has been reported able to clear the central nervous system of borreliae and to reduce the relapse rate. The originally recommended treatment schedule was first 0.2 Gm, then 0.5 Gm for one or two days, to a total of 4 Gm in 3 to 4 days; later 0.5 Gm every 6 hours for 6 to 7 days, or 0.25 Gm weekly to reduce the chance of relapses.

Bryceson *et al.* (127) prefer intravenous instead of oral administration of tetracycline because their patients often suffer from vomiting. One-quarter of a Gm is injected, over a period of 2 to 3 minutes. Borreliae disappear from the blood within 2½ hours. The administration of 0.15 Gm in 6-hour intervals has also been helpful. Bryceson *et al.* administer 4.5 to 5.5 Gm per os over 4 to 5 days but they have observed no relapses after a single injection of 0.25 Gm, without additional tetracycline administration.

A careful approach to therapy is indicated because possible unfavorable reactions to the treatment are not infrequent, principally when a potent drug is administered late in the disease. Parry *et al.* (562), Schofield *et al.* (629), and Bryceson *et al.* (127) described sudden rise in temperature, increase in pulse and respiration, and subjective discomfort after tetracycline administration in some patients. After the first phase of the reaction, the temperature usually decreases by lysis. This is accompanied by a fall of the blood pressure, and a decline in the number of white blood cells. These authors studied the hemodynamic and allied changes in great detail. The reaction appears to be biphasic, which led this group of investigators to the interesting conclusion that it may be due to the liberation of endogenous toxin from leukocytes. Similar reactions have been observed after the administration of other antibiotics (631) and convalescent serum (65).

In epidemics, when careful individual attention cannot be given to every patient, Bryceson *et al.* (127) have proposed the use of 300,000 U procaine-penicillin intramuscularly, and then on the next day to give orally 0.25 Gm tetracycline. Procaine-penicillin, 80,000 units intramuscularly every 6 hours in 1¼ days has been recommended by these authors when development of a Jarisch-Herxheimer reaction is feared.

Data on other antibiotics and comparison of various drugs have been published by several writers (266, 267, 631, 709 and others).

Convalescent serum, 20 ml intravenously, has been of little value to Adler and Ashbel (3) but was considered helpful by Balteanu *et al.* (65), Gaud and Morgan (298), and Sergent (639). Jarisch-Herxheimer type reactions were frequent. Moreover, "safe" convalescent serum (free from infectious agents, especially of viral and rickettsial nature) is seldom available during epidemics.

Jarisch-Herxhemier Reaction

One of the most unpleasant side effects of medication with arsenicals used to be the Jarisch-Herxheimer reaction, principally in diseases caused by Treponemataceae. Whereas in syphilis or pinta, where the number of organisms is relatively small, the sudden disintegration of the treponemas did not cause serious disturbances as a rule, being only a short exacerbation of the cutaneous symptoms with transient fever, the Jarisch-Herxheimer reaction has been

a serious complication of the administration of arsenicals in borreliosis. This is due to the fact that large numbers of borreliae disintegrate simultaneously and suddenly. Originally believed to be due to liberated toxin, Parry *et al.* (1967) and Schofield *et al.* (1968) showed that the Jarisch-Herxheimer reaction in relapsing fever after tetracycline administration is allied with ventilation and hemodynamic changes different from those caused by endotoxins. The oxygen intake is increased. Arterial blood bicarbonate decreases as a result of impaired pulmonary gas exchange. Blood lactic acid is increased. The cardiac output remains high, indicating hypotension resulting from low systemic vascular resistance, at the same time pulmonary arterial pressure is increased. The administration of pure oxygen does not alter the changes in ventilation and circulation but favorably influences lactic acidosis. This may be a sign of tissue hypoxia. The lack of a favorable effect of hydrocortisone that acts as a stabilizer is also of interest. During recovery from the reaction, the mean pressure in the brachial artery remains low but cardiac output is still increased. Thus the study of the Jarisch-Herxheimer reaction in relapsing fever is unfolding new concepts of this syndrome.

Supportive Therapy

Bed rest is recommended. Sponging with cool (not hot) water is helpful.

It is necessary to restore the fluid and electrolyte balance of the patient, if it is disturbed. The venous blood pressure should serve as an indicator, as well as blood chemistry. Adrenergic vasopressor drugs must be used cautiously, to prevent diminished heat unloading during the high fever because of the vasoconstriction of the dermal vessels induced by such pharmaceuticals (127).

Schofield *et al.* (629) did not observe favorable results using hydrocortisone after the Jarisch-Herxheimer reaction developed but are in favor of administering 20 mg per Kg body weight 4 hours before tetracycline treatment.

It is customary to give vitamin K against bleeding. The usual dose is 20 mg intramuscularly.

Symptomatic treatment is often indicated, and should follow the general rules of the therapeutic indications and contraindications

for the selected procedures. For instance, nausea and vomiting may require the administration of dimenhydrinate (Dramamine), 50 mg intramuscularly. Intensive pain may be alleviated by analgesics.

Prevention

Vaccines and Drugs

Aristowsky and Wainstein (25) experimented with a vaccination method consisting of injecting the blood of infected animals previously heated at 60° C for 30 minutes. It protected only against the homologous strain. Russell (619) was able to prevent *Borrelia* infections in rats by administering killed organisms together with immune serum. Sergent (639), using *B. hispanica,* could evoke premunition lasting two years with freeze-killed organisms and with bile vaccine.

Nevertheless, vaccines against borreliae for human use are not yet available. The serologic differences of the strains and their phase variations during relapses militate against the development of an effective immunizing agent.

In Tanzania, Geigy (303) observed laborers from Rwanda who carried *O. moubata* with them and permitted these ticks to feed on them periodically so as to preserve their immunity to relapsing fever. However, this method is not quite applicable to other population groups.

Drug prophylaxis trials with an antibiotic have not yet been reported but they could be considered on a theoretical basis for persons exposed to the infection for a short time only.

General Measures

Disinfection of clothing with the aid of dry heat in "delousing stations", cutting hair short, and shaving the body have been time-honored measures to prevent the multiplication and survival of lice. In addition to these procedures, Hunter (377) in Serbia during the First World War stopped railway traffic and reduced the movement of the populace to a minimum, as a general measure to halt the spread of *Borrelia*-bearing lice.

The Administration in South Africa forbade indigenous people to carry their bundles into tick-free houses, and recommended the building of cement resthouses for travelers.

Some general measures were used in the Indian Army after World War I (717). These consisted of washing or bathing twice daily, spreading the clothing on the hot sand in the sun; then taking it to a different place to be shaken out; posting guard against villagers so as to avoid contact with the organisms or their vectors; getting close haircuts if the caste permitted it; keeping out of huts and caves but staying under canvas; and turning the tents inside out during the day. This procedure was an effective preventive measure.

In Africa, the following measures were recommended (467): avoiding huts, especially those with earthen and cow dung floors; keeping out of camp sites previously used by the local population; searching lodgings for ticks; inspecting blankets of the soldiers for *Ornithodoros;* and offering a small award (one penny or so) to local children for each tick collected.

Vector Control

Dry heat and a number of chemicals kill arthropods (see above) but they withstand home illumination and ultraviolet light (364, 414).

Vectors of *Borrelia* are sensitive to DDT* dusting powder, 5 to 10%, that has proved effective against lice (251, 296). It is applied to the clothing. About 40 to 50 Gm of the powder are required for each person. Bed linen and clothing can be impregnated with a 1% DDT emulsion, using 6 volumes of emulsion for each volume of linen or clothing. In certain areas, however, lice have become resistant to DDT (135). Other dusting powders have also been considered, but 0.5 to 1% of the gamma isomer of benzene hexachloride (Gammexane®, BHC) is frequently recommended as well as 1% lindane dust. Diazonium polychlorides appear effective. Pyrethrum is used as a 0.25% powder. The effect of these contact insecticides lasts from one to several weeks.

Progress in methods used to exterminate tick vectors has been summarized by Walters (709) and Arthur (26, 27). One single spray of 3% BHC in diesoline, 600 mg per sq. ft., kept huts and coffee shops free from *Ornithodoros* for 27 months in East Africa (16). A 5% mixture of BHC in sawdust, laid in 4-inch wide bands around the base and doorwalls of the huts, kept ticks away for

*Some governments are discouraging the general use of DDT.

3 months. Tesdale (677) observed similar results. Annecke and Quinn (19) employed a 17% emulsion of 4% BHC. Less effective is the frequently used 1% dust, about 10 Kg per 100 sq. m. Holmes (370) was satisfied with 40% wettable cattle dipping powder with 5% BHC. In urban Somaliland, residual sprays of BHC, 15 mg per sq. ft., in two applications 4 to 6 months apart, were effective (461).

Pospelova-Shtrom (587) reported favorable results in Central Asia with applications of 2 Gm BHC per sq. m. in houses, and 6 to 8 Gm per sq. m. in sheds, approximately every 6 months, for 2 years. The timing of the spraying should coincide with the hatching of developmental forms of *Ornithodoros* and with the first appearance of ticks in the spring. She also stated that larvae and early nymphs are susceptible to DDT which may be used in antimalarial campaigns in the same area.

Jepson (385) recommended BHC against *O. moubata* and reported that 80 to 100% were killed in 8 to 10 days after 0.5% dust had been used. In surviving females, the eggs did not hatch. In his experience, 5% DDT powder also destroyed 50 to 80% of the ticks in about 50 days. Approximately 3 to 4 lbs were used for each 1,000 sq. ft. The floors of the huts and camps were dusted, as were a few inches of the bottoms of the walls. Re-treatment was needed every 9 months. To reduce costs, Jepson used 2.5% commercial Gammexane dust and diluted it with locally available diatomaceous earth. The final cost was about 4¼ cents per lb.

Fendall and Grounds (269) and Tesdale (678) were satisfied with the long-range effect of residual BHC application against *Ornithodoros.*

The tarring of wood cabins has been recommended to repel ticks. Leaving lights on during the night might deter any *Ornithodoros* with nocturnal habits.

Attempts to reduce the tick population by biological means are being made on an experimental scale.

Teravskii (679) studied *O. tholozani.* The ticks were exposed to 10,000 r from a ^{60}Co source that did not kill adults or nymphs of the F_3 and F_4 generations. Two thousand r, however, were lethal for larvae and the first nymphs. The irradiated adult females did not lay viable eggs. Galun *et al.* (289) studied the relationship

of sexual competition in irradiated *O. tholozani* males. After 2,000 r, the males were not competitive, because of the lack of sperm. Females were sterilized with as little as 100 r. A 99% genetic lethal result could be induced by radiation, after adding sterile individuals to nonsterile tick populations. This method of insect control, particularly using competitive sterile males, was effective in reducing the tick population in caves.

Tick extermination is not practical in sparsely inhabited areas. An insect repellent is recommended for use of those who enter caves or abandoned huts, or who work around animal burrows. Dimethyl phthalate, copper oleate, benzyl benzoate, dibutyl phthalate, and diethyl lauramide have been recommended for impregnation of the clothing. Dimethyl phthalate has been extensively tested. It is often used in 5% concentration in a 2% oil emulsion. Washing with 10% carbol soap is also effective.

National and International Measures

Measures taken against relapsing fever vary from country to country. It is generally conceded that little can be done to prevent tick-borne *Borrelia* infections outside human habitations except by the use of repellents.

International Sanitary Regulations (379) require notification of cases of louse-borne relapsing fever and direct disinsection of persons arriving from infected areas before they are permitted to enter into international travel. The requirement that a passenger be free of such ectoparasites is a general health and esthetic demand. On the other hand, persons with bad hygienic habits, principally in dry and cold areas, usually move from one place to another as migrants and often cross borders illegally or without the benefit of medical inspection and examination. Despite all this, louse-borne relapsing fever has not spread in the recent past except in the Sudan and when large movements of destitute populations, dislocated by war, famine, floods, earthquakes, and other disasters, have been coupled with crowding and lack of personal hygiene. It seems obvious that surveillance of areas where migrating tribes or other groups of people move about and of neighboring territories where they visit or settle might offer better insurance against the development of relapsing fever epidemics than the international measures

alone that are presently recommended. Improvement of personal hygienic practices as a result of properly conducted public health education may yield far-reaching benefits. Naturally, good results cannot be achieved through the limited medical means available to a stricken country during a national disaster, nor can the endemic focus in Abyssinia be eradicated with ease.

The problem of tick-borne relapsing fever as a disease in which animals play a role is not sufficiently emphasized in most texts. Admittedly, mammals play a limited role in the maintenance of several tick-borne borreliae. Nevertheless the habits of some ticks of associating with domestic animals is widespread and deserves more extensive study, particularly in areas where *Ornithodoros* is becoming domesticated or where it is attracted by horses, camels, cows, sheep, goats, pigs, dogs, and other animals that are in contact with man.

The story of the spreading of *O. tholozani* with camels and sheep, and the recent observations in Texas and Mexico of at least two species of *Ornithodoros* that have become domesticated show that more life science researchers, including veterinarians, must be allerted to the possibility that relapsing fever-carrying ticks are in their area, and such researchers should be encouraged to cooperate in the eradication of tick-borne relapsing fever. It could also be expected that if hunters, soldiers, vacationers, and other persons who enter tick-infested areas are educated to the possibilities of *Ornithodoros*-borne relapsing fever, this could help to reduce the number of such infections.