

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 Bryceon *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 borreliæ 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). Borreliæ 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. duttoni* 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.

Borreliæ 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 borreliæ, 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), Bryceon *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 crociduræ 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 crociduræ 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. hermsii* 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.

Wynn (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,

