RELAPSING FEVERS. A REVIEW
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1. Introduction

Relapsing fever (RF) is a forgotten illness. The lack of interest for this disease is clearly shown by the few original papers on the subject. A revived interest is necessary to stimulate research in this field where numerous gaps persist in our knowledge (Burgdorfer, 1976b; Janssens, 1983). Since the general reviews by Southern and Sanford (1969) and Felsenfeld (1971) and that on louse-borne relapsing fever by Bryceson et al. (1970), some interesting work has been done especially in the fields of pathophysiology, immunology and bacteriology. The purpose of this paper is to describe our present knowledge by reviewing the literature of the last 15 years. General information has been borrowed from the above-mentioned reviews and the reader is referred to these and to the review on the epidemiology by Rodhain (1976) for further details about previous work and long established facts. Specific reference to these papers is only given when specific facts or opinions are mentioned.

Relapsing fever is an infectious disease caused by different Borrelia species, which give an intense bacteriæmia (often up to 300,000 organisms/mm$^3$). It is characterised by episodes of fever separated by afebrile intervals. On the basis of their vector RFs are divided into louse-borne relapsing fever (LBRF) and tick-borne relapsing fevers (TBRF) transmitted by various soft ticks of the genus Ornithodoros. Most TBRFs are zoonoses.

2. Bacteriology

2.1. Taxonomy

The classification of borreliae and more generally of the spirochaetes is the subject of frequent changes, illustrating the incompleteness of our knowledge. Several classifications of the order Spirochaetales have been proposed during the last 15 years (Smibert, 1974; Willcox, 1976; Hovind-Hougen, 1976b). Presently the following taxonomy is proposed in « Bergey's Manual of Systematic Bacteriology »: the order Spirochaetales Buchanan, 1917, is divided into two families, the Spirochaetaceae Swellengrebel, 1907, with the genera Spirochaeta Ehrenberg, 1835, Cristispira Gross, 1910, Treponema Schaudinn, 1905, Borrelia Schwellengrebel, 1907, and the Leptospiraceae Hovind-Hougen, 1979, with the genus Leptospira Noguchi, 1917 (Canale-Parola, 1984).
Borreliae can be differentiated in practice from other pathogenic spirochaetes by the fact that they stain easily with ordinary aniline dyes. Electronmicroscopy also presents some characteristics typical of borreliae: they have sharply pointed ends, they have no cytoplasmic tubules and possess 15 to 30 unsheathed flagellae at each end (Hovind-Hougen, 1976b) (see 2.4.).

The different relapsing fever Borrelia species are identified mainly on the identity of their arthropod vector, their pathogenicity for laboratory animals and their geographical distribution. These criteria do not give a clearcut separation in species and strains and this explains the different synonyms and overlapping of species one can find in the literature. There have been some attempts to find biochemical and morphological criteria as an aid to classification (Hovind-Hougen, 1974, 1976b; Smibert, 1976; Karimi et al., 1979) (see 2.4. and 2.6.) but further similar studies are required on the different known species of borreliae to arrive to generally valid conclusions. A recent study of the DNA base content (guanine-plus-cytosine) and of the DNA relatedness by DNA hybridisation of the three North American borreliae concludes that these 3 borreliae in fact constitute a single species (Hyde & Johnson, 1984). The different species with their vector and geographical distribution are presented in table 1.

2.2. Relationship Borrelia — arthropod vector

2.2.1. Louse

*B. recurrentis* is transmitted by *Pediculus humanus*. After ingestion by the louse the spirochaetes pass from the gut into the coelomic cavity, where they multiply. The louse remains infected for life, which lasts several weeks. It cannot transmit the disease by biting or through excrement but infection occurs by contamination of abraded or normal skin or mucous membrane by hemolymph from crushed lice. Before multiplying in the coelomic cavity the few borreliae are difficult to find: this has been called the «negative phase» in past publications.

Several species of tick-borne borreliae can experimentally be transmitted to lice (see 3.2.).

2.2.2. Ornithodoros

The ticks that transmit RF are *Argasidae* of the genus *Ornithodoros*. Development of the spirochaete in the tick has been most extensively studied in *Ornithodoros moubata*. A few hours after ingestion of an infective blood meal by *O. moubata*, the spirochaetes accumulate along the gut wall, penetrate into the hemocele and multiply there. Within 3 to 4 days they invade the salivary glands, coxal glands, central ganglion and the Malpighian tubules. Five to six days after an infective blood meal the ticks become infectious. In *O. moubata*, nymphae and young adults transmit the infection during their blood meal by saliva, while adult forms essentially transmit the infection by coxal fluid. Other ticks like *O. tholozani*, *O. hermsi* and *O. turicata* transmit the infection only by saliva because they secrete only minute amounts of coxal fluid which crystallizes on the tick or because they leave their host before emitting the fluid (Rodhain, 1976; Burgdorfer, 1976a).
<table>
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<th>Borrelia species</th>
<th>Vector</th>
<th>Geographical area</th>
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<tr>
<td>Louse-borne relapsing fever</td>
<td></td>
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<tr>
<td><em>B. Recurrentis</em> (= <em>B. novyi</em>)</td>
<td><em>Pediculus humanus</em></td>
<td>Virtually cosmopolitan Presently known distribution: Ethiopia, Sudan</td>
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<td>Tick-borne relapsing fever</td>
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<tr>
<td><em>B. duttonii</em></td>
<td><em>Ornithodoros</em> species</td>
<td>East and Central Africa, Madagascar</td>
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<tr>
<td><em>B. hispanica</em></td>
<td><em>O. moubata</em></td>
<td>Spain, Portugal, Maghreb, Greece, Cyprus, Syria (?)</td>
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<tr>
<td>Crociduridae group</td>
<td></td>
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<tr>
<td><em>B. crocidurae</em></td>
<td><em>O. erraticus erraticus</em></td>
<td>North and South of Sahara from West Africa to North-East Africa, Middle East to Iran</td>
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<tr>
<td><em>B. meriones</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>B. microti</em></td>
<td></td>
<td></td>
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<tr>
<td><em>B. dipodilli</em> (and others ± well defined)</td>
<td></td>
<td></td>
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<tr>
<td><em>B. persica</em> (and related species or strains)</td>
<td><em>O. tholozani</em> (= <em>O. papillipes</em>)</td>
<td>South USSR, Iran, Middle East Cyprus, Afghanistan (?), Egypt (?), Libya (?)</td>
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<tr>
<td><em>B. uzbekistanica</em></td>
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<td><em>B. sogdiana</em></td>
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<td><em>B. babylonensis</em></td>
<td><em>O. asperus</em></td>
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<td><em>B. turkmenica</em></td>
<td><em>O. cholodkovskyi</em></td>
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<td><em>B. latyshewii</em></td>
<td><em>O. tartakowskyi</em></td>
<td>Central Asia</td>
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<td><em>B. caucasia</em> (= <em>B. armenica</em>)</td>
<td><em>O. verrucosus</em></td>
<td>Caucasus, Armenia, Azerbaijan, Georgia</td>
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<td><em>B. hermsi</em></td>
<td><em>O. hermsi</em></td>
<td>Western USA, British Columbia</td>
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<td><em>B. parkeri</em></td>
<td><em>O. parkeri</em></td>
<td>Western USA</td>
</tr>
<tr>
<td><em>B. turicatae</em></td>
<td><em>O. turicata</em></td>
<td>Texas, Kansas, Mexico</td>
</tr>
<tr>
<td><em>B. venezuelensis</em> (= <em>B. neotropicalis</em>)</td>
<td><em>O. venezuelensis</em></td>
<td>Panama, Colombia, Venezuela, Ecuador, Paraguay</td>
</tr>
<tr>
<td><em>B. mazzottii</em> (and other unnamed borr.)</td>
<td><em>O. talaje</em> (?)</td>
<td>Central and South America</td>
</tr>
<tr>
<td><em>B. dugeesi</em></td>
<td><em>O. dugeisi</em></td>
<td>Central and South America</td>
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Ref.: Southern and Sanford, 1969; Felsenfeld, 1971; Rodhain, 1976.

Transovarial transmission of borreliae to the offspring with varying rates has been demonstrated in *O. moubata*, *O. erraticus* (both varieties), *O. tholozani*, *O. tartakovskyi*, *O. verrucosus*, *O. turicata*, and *O. hermsi*, but does not occur in *O. parkeri*, *O. talaje* and *O. rudis* (Burgdorfer, 1976a).

Venereal transmission of borreliae by infected males to uninfected females occurs in *O. erraticus* and to a lesser extent in *O. moubata* (Gaber et al., 1982).

2.3. Susceptibility of laboratory animals

Inoculation of animals is useful to identify *Borrelia* species, to maintain the organism in the laboratory and to study the pathophysiology of the disease. In animal experiments it is essential to specify the age of the tested animal, the route of administration and the type of infection that follows. Failure to provide this information has caused much confusion in the past (Felsenfeld, 1971; Rodhain, 1976).

Monkeys, mice, rats, rabbits, guinea pigs, hamsters and hedgehogs have all been used to test borreliae. A detailed study of the clinical course, the pathology and the reaction to treatment in *B. recurrentis* infection of grivet monkeys (*Cercopithecus aethiops*) showed the infection to be similar to that in man, providing a good (though expensive) model for experi-
mental work (Judge et al., 1974 a, b, c). The susceptibility of a given laboratory animal can sometimes be enhanced by passage of the borrelia through another animal; for instance the passage of B. recurrentis in a rabbit or a monkey enhances its virulence for adult mice. Details on the susceptibility of laboratory animals to different species of Borrelia can be found in the review by Rodhain (1976).

A characteristic that may be of help in the identification of a Borrelia strain is its ability to protect animals against simultaneous infection with trypanosomes (Felsenfeld & Wolf, 1973; Rodhain, 1977) (see 5.3.).

Another characteristic of some borreliae (e.g. B. duttonii) is their ability to give a latent brain infection in laboratory animals.

2.4. Morphology

Borreliae are slender spiralled organisms, 10 to 20 micron long and 0.2 to 0.6 micron wide, with 3 to 15 windings. The morphology as seen with the lightmicroscope is partly dependent on fixing and staining techniques. On bloodsmears the organisms appear loosely and irregularly coiled, clumping together when numerous. In fresh wet preparations borreliae are actively motile, moving in the direction of either end by rotational or corkscrew manoeuvres, lateral bending or flexing or wave-like motion.

Electron microscopic studies have brought some new elements on the ultrastructure of borreliae. The borreliae are right-handed helical cells (Stepan & Johnson, 1981) with pointed ends, covered by a cytoplasmic membrane, an outer membrane and a surface layer (amorphous for B. recurrentis, B. merionesi, B. balthazardi, and structured for B. persica). Near each end of the cell 15 to 30 flagellae are inserted (also named fibrils or axial filaments). From there they wind around the cytoplasmic body between the cytoplasmic and outer membrane, overlapping in the middle. The insertion points with basal bodies are arranged in a row following the helical structure of the cell. The flagellae are similar to those isolated from various species of Treponema, Spirochaeta and Gram positive bacteria, but they are unsheathed. The cells do not contain cytoplasmic tubules differing in this respect from Treponema. In the cytoplasm the skeinlike nuclear area is situated in the middle of the cell, while ribosomes are distributed at the periphery (Hovind-Hougen, 1974, 1976 a, b; Karimi et al., 1979).

It is not possible to differentiate Borrelia species by electronmicroscopy for most seem quite identical, but some differences in number of flagellae (Karimi et al., 1979; Klaviter & Johnson, 1979), in mean dimensions and in the structure of the surface layer have been observed between some species (Karimi et al., 1979). On the other hand, in the same species variations of the morphology as seen with the lightmicroscope have been observed: the mean length of B. duttonii is said to differ according to the geographical area, measurements are variable with the immune and chemotherapeutic status of the host and variations in morphology occur when organisms are transferred to different hosts. In Kelly's culture medium the length of B. hermsii is influenced by the number of passages, the age of the culture and the size of the inoculum (Stoenner, 1974).

Multiplication of Borrelia occurs by binary transverse fission. The earliest sign is a constriction of the cytoplasmic body in the middle of a long
cell, while new flagellae appear, inserted at each side of the constriction. After complete separation of the cytoplasmic membranes the two ends appear at first truncated, but become tapered while still connected by a common outer membrane and finally separate (Hovind-Hougen, 1974).

In the past a «granular form» gave rise to the «granule theory»: a metacyclic development was put forward to explain the disappearance of the borreliæ from the blood between attacks and from the gut of the vector before appearing in the coelomic fluid. In fact these granules are degradation products and it is not believed that borreliæ undergo an evolutionary life cycle in the vector or in the host (Bryceson et al., 1970; Felsenfeld, 1971).

2.5. Cultivation of Borrelia

Apart from maintaining borreliæ in their vector (survival of borreliæ in ticks has been reported for periods up to 12 years without loss of infectivity), or by regular passage in susceptible laboratory animals, borreliæ have been successfully propagated in the chorioallantoic membrane of developing chick embryos.

Since the beginning of this century several artificial culture media have been developed for Borrelia with unsatisfactory results, until Kelly (1971) developed a successful culture medium (medium A) for B. hermsii, which gives a maximum yield of $3-5 \times 10^7$ organisms/ml with a generation time of 18 hours. Eight hundred spirochaetes are necessary for initial isolation but a single organism of a fully adapted strain is sufficient for subculture (Stoenner, 1974). Stoenner et al. (1982) modified the medium to a «fortified Kelly's medium» which allows growth from a single borrelia and allows expression of the surface antigens of different variant strains (see 4.3.). Cultured borreliæ have retained infectivity for mice for over 100 subcultures, but with more prolonged in vitro cultivation (over 150 subcultures) there is attenuation and infectivity is lost (Kelly, 1984). This medium also permits transmission of B. parkeri, B. turicatae (Kelly, 1976), B. duttonii (Kelly, 1984) and of the spirochaetes that cause lyme disease, possibly another tick-borne borreliosis (Hyde & Johnson, 1984).

Another medium (Kelly's medium B) sustains growth of B. hispanica to a relatively low level ($7 \times 10^8$/ml) with successful subcultures, retaining infectivity for guinea pigs (Kelly, 1976).

Growth of B. recurrentis in modifications of Kelly's A medium is limited and subculture is impossible (Dodge, 1973a). Another medium (Kelly's medium C) gives relatively low growth levels (maximum yield of $5 \times 10^8$/ml with a generation time of 24 hours) but allows subcultures. No data on infectivity of the cultured organisms are available (Kelly, 1976).

Borrelia organisms can be stored at $-70\degree C$ in infected plasma to which glycerin has been added to a final concentration of 10 per cent (Kelly, 1976).

2.6. Biochemistry

Only sporadic data on the biochemistry of RF borreliæ are available and the present knowledge is often the result of extrapolation of the findings in a few species studied.
The borreliae that have been cultivated are micro-aerophilic (Kelly, 1971). They utilise mainly glucose as source of energy, producing lactic acid as the main end-product of fermentation (Smibert, 1976). A study of North American borreliae showed that *B. turicatae* ferments glucose, raffinose, and dextrin, while *B. hermsii* and *B. parkeri* ferment glucose, maltose, trehalose, starch, dextrin and glycogen. Borreliae do not use fatty acids as a major source of energy. They hydrolyse fatty acids from lyssolecithin but cannot metabolise other major phospholipids or triglycerides. Fatty acids can serve as the sole lipid nutrient for *B. hermsii* in culture media lacking lyssolecithin or rabbit serum (Pickett & Kelly, 1974), but it is necessary to provide a mixture of both saturated and unsaturated fatty acids (Kelly, 1976). Cholesterol is a constituent of RF borreliae and studies with *B. hermsii* have shown that cholesterol is selectively removed from the culture medium during growth (Pickett & Kelly, 1974). The organisms have the ability to synthesize lecithin (Pickett & Kelly, 1974). The lipid composition of borreliae is similar to that of treponemes with phosphatidylcholine and the glycolipid monogalactosyl diglyceride as the major constituents (Johnson, 1977). Alpha-glycerophosphatase dehydrogenase activity, allowing the exchange of three-carbon components between the pathways of carbohydrate and lipid metabolism, has been detected in *B. duttonii* in the past but could not be found in *B. hermsii*, making *B. hermsii* more dependent on its host for certain nutrients (Pickett & Kelly, 1974).

The presence of plasmid DNA has been detected in the three North American borreliae, suggesting their potential to develop plasmid-mediated biological properties (Hyde & Johnson, 1984).

2.7. Phylogeny

According to the generally accepted hypothesis RF borreliae were probably since the origin symbionts of *Ornithodoros* and evolved together with the ticks while these adapted to different biotopes and became different species and strains. The extraordinary sedentary of the ticks explains their independent evolution to a multitude of strains, each with its own borrelia. These borreliae adapted also to the vertebrate hosts of their vector, one of these being man. From man secondary adaptation probably occurred to lice giving rise to *B. recurrentis* (Felsenfeld, 1971; Hoogstraal, 1979).

3. Epidemiology

3.1. Transmission

Normally RF is transmitted by a vector, louse or *Ornithodoros* tick. The louse only transmits the infection if injured or crushed. Transmission of lice from person to person occurs in circumstances of promiscuity and low personal hygiene. Lice tend to leave the body when there is high fever, thus favouring transmission when there are many symptomatic infections, like during an epidemic (Burgdorfer, 1976a). The *Ornithodoros* tick transmits the infection by saliva or coxal fluid during nocturnal feeding on an animal or human host.
Other modes of transmission include transplacental infection (see 5.5.), accidental infection of laboratory workers (Favorova et al., 1971) and transfusion of infected blood (Hira & Hussein, 1979).

3.2. *Louse-borne relapsing fever* (LBRF)

LBRF is virtually cosmopolitan having caused large epidemics, characteristically in the wake of largescale disastrous events. Overcrowding, cold weather, lapses in personal hygiene and malnutrition are factors associated with a high incidence of LBRF. The same factors also favour typhus, another louse-borne disease, and both illnesses have often occurred together. Typically the LBRF epidemic appears after the beginning of the typhus epidemic and ends later (Rodhain, 1976). The last large-scale epidemic occurred during and just after World War II with about 10 million cases (Bryceson et al., 1970). Presently LBRF is found in Ethiopia and the Sudan (and possibly in mountainous areas of South America; Burgdorfer, 1976a) as an endemic disease with sporadic cases and local epidemics. Abdalla (1969) showed that the infection is in fact wide-spread in the population, existing largely as asymptomatic infections and mild forms of the disease.

In the past many authors felt that the mysterious reappearances of the disease indicated either an animal reservoir or a transformation of tick-borne borreliae into louse-borne borreliae. No naturally occurring *B. recurrentis* animal reservoir has been found (Bryceson et al., 1970). Most tick-borne borreliae have been experimentally transmitted to lice and several have been shown to multiply in lice. Heisch (cited by Rodhain, 1976) found *B. duttonii* infected lice on RF patients in Kenya. On the other hand mutation of a tick-borne borrelia to a louse-borne form has never been proven. The antigenic stability of borreliae in arthropods is much greater than in animals, making repeated transmission cycles probably necessary to establish variants and mutants with genetically modified characteristics (Felsenfeld, 1971).

After multiple passages through lice (from 6 to 30 times over 2.5 years) *B. sogdiana* still provokes an infection in all respects identical to TBRF in animals as well as in humans (Favorova et al., 1971; Chernyshova & Favorova, 1971). LBRF also appeared in places where no TBRF is known to be present, like in Vietnam some years ago (Burgdorfer, 1976a). All these facts indicate that lice could perhaps participate in the transmission of borreliae in a focus of TBRF, but there is no evidence to admit that a tick-borne borrelia can be transformed to a louse-borne borrelia. The present persistance of foci of LBRF with many asymptomatic carriers is certainly a greater hazard for a new large-scale epidemic.

3.3. *Tick-borne relapsing fevers* (TBRFs)

3.3.1. General aspects

TBRF is widely distributed in disseminated foci around the world (see table 1). The epidemiology of TBRF is dependent on the tick vector and its degree of infection, on the natural host (often wild rodents), and on the possibility of contact between man and the vector. Infection occurs
when humans sleep in the vicinity of infected *Ornithodoros* ticks: the
ticks are indeed nocturnal feeders and are very sedentary, living within a
radius of 30 meters, further displacement being due to human action
(Janssens, 1982). The incidence of RF varies widely from one focus to
another. Even in periods of low transmission, a focus can persist for years,
owing to the fact that the ticks can remain infective for several years even
without feeding, that some can transmit the infection to their offspring
and some transmit borreliae during copulation.

There is an extraordinary geographical variation of borreliae and their
*Ornithodoros* tick even within one species, with a high tick-borrelia spe-
cificity, although this is not absolute in experimental conditions.

Owing to modern travel RF can be found outside its distribution area,
making the diagnosis still more difficult: during the past 15 years there
have been case reports of RF from the Eastern United States (Goodman
*et al.*, 1969), France (Lavarde *et al.*, 1975; Gentilini *et al.*, 1978) and The
Netherlands (Van der Heide, 1971).

### 3.3.2. African TBRFs

Three *Ornithodoros-Borrelia* complexes can be found in Africa: *O.
moubata* and *B. duttonii* in East and Central Africa; *O. erraticus erraticus*
and *B. hispanica* in the Maghreb countries, Spain, Portugal, Chyprus and
Greece; *O. erraticus sonrai* and borreliae of the «crocidurae» group
extending from West Africa to North and North-East Africa and further
through the Middle-East to Iran.

In the wild, *O. moubata* lives in large animal burrows of antbears,
warthogs and porcupines and has adapted secondarily to human dwellings
and domestic animal shelters, where it lives in the cracks of walls and
floors. According to the work of Walton (cited by Rodhain, 1976) what is
known as *O. moubata* constitutes in fact a complexe of four species with
only the first two having an epidemiological importance: *O. moubata ss,
O. porcinus, O. apertus* and *O. compactus*. Due to differences within this
« *O. moubata* complex », RF by *B. duttonii* may present as sporadic cases
in some parts of its area, while in other places it is a highly endemic
disease. No animal has ever been found naturally infected by *B. duttonii*,
nor any tick living outside the neighbourhood of humans. Man and
*O. moubata* thus constitute the only known reservoirs of this infection.

*B. hispanica* is transmitted by the large variety of *O. erraticus, O. e.
erraticus*. Rats constitute the main reservoir.

The «crocidurae » group consists of a mosaic of *Borrelia* strains with
similar biological properties and which are transmitted by the small variety
of *O. erraticus, O. e. sonrai*. These borreliae differ from *B. duttonii* by their
pathogenicity for young guinea pigs, but some confusion between these
two species can be found in older literature. Several species names have
been given to different geographical groups (table 1). *O. e. sonrai* lives in
rodent burrows of savannah and semi-desert areas. When rodent holes
extend to houses, human RF cases occur. Quite frequently, sporadic cases
of a mild RF can be found throughout the distribution area (Janbakhsh &

The relative importance of different African TBRFs can be illustrated
by the following examples: in a focus of *B. duttonii* RF in Rwanda a mean
of 1,650 cases of microscopically confirmed infections are treated each year in one health centre, representing about 6 per cent of all patients (Zaza Health Centre, E. de Pierpont, personal communication), while Aubry et al. (1983) could find only 14 cases of *B. crocidurae* RF over a 9 months study period in Dakar.

### 3.3.3. Asian TBRF

In Asia several *Ornithodoros-Borrelia* complexes can be found. The «crocidurae» group has already been described with the African TBRF. The other most important group is constituted by *B. persica* whose usual vector is *O. tholozani*. Like for the «crocidurae» group the taxonomy for *B. persica* is extremely complex and Rodhain (1976) groups under this binome a number of closely related species or strains:

- *B. uzbekistanica*
- *B. sogdiana*
- *Borreliae* spp from Cashmire and Penjab
- two related complexes formed by *B. babylonensis* transmitted by *O. asperus*, and *B. turkmenica* transmitted by *O. cholodkovskiyi*.

Together these borreliae cause RF in an area extending from Chyprus and the East Mediterranean (with perhaps Egypt and Lybia) to Iran, Southern USSR and possibly Afghanistan and Pakistan.

Another borrelia, *B. caucasica*, transmitted by *O. verrucosus* gives a clinically serious RF in Azerbaijan, Georgia and Armenia.

*B. latyshevii* transmitted by *O. tartakowskyi* gives a very mild or asymptomatic infection without relapses. *O. tartakowskyi* lives in semi-desert areas of Iran and Central Asian USSR.

Epidemiological investigations showed the persistance of infected ticks (*O. tholozani* and *O. tartakowskyi*) in Central Asian USSR, although no human cases have been reported in recent years (Balashov, 1972; Ershova & Vasilieva, 1982; Reznik et al., 1983).

A focus of possible RF has been described by Karimi et al. (1976) in Iran, which long had been considered as a focus of viral haemorrhagic fever. They isolated from a patient a borrelia that differs from *B. persica* in its pathogenicity for animals and its morphology as seen by electronmicroscopy, and which was named *B. balthazardi* (Karimi et al., 1979).

### 3.3.4. North American TBRF

*O. hermsi*, vector of *B. hermsii*, is found in the western United States and British Columbia. *O. parkeri*, vector of *B. parkeri*, is distributed in the same area, but while *O. hermsi* is usually found at elevations above 1,000 meter and parasitizes chipmunks, tree squirrels and pine squirrels, *O. parkeri* inhabits caves and burrows of ground squirrels and prairie dogs and is not found at high elevations. *B. turicatae* transmitted by *O. turicata* is the principal RF borrelia in Texas and Kansas. *O. turicata* is found in caves, rodent, owl and snake burrows and under houses (Thompson et al., 1969).

*B. hermsii* is certainly the most important RF borrelia in North America and regularly causes sporadic cases (Fuchs & Oyama, 1969; Gatlin, 1977; Malison, 1979; Edell et al., 1979) and small outbreaks (Thompson et al.,
1969; Boyer et al., 1977). The largest outbreaks ever recorded occurred in 1973 at Grand Canyon National Park with 62 possible and 16 confirmed cases among visitors and park employees (Boyer et al., 1977). In the two outbreaks reported in the last 15 years, the illness was contracted by sleeping in old cabins whose walls contained numerous rodent nests with infected ticks. The Grand Canyon outbreak was caused by an increased activity of ticks among humans, due to a greatly diminished rodent population after a bad winter (Boyer et al., 1977) and a plague epizootic (Burgdorfer, 1976a).

The first case of RF contracted in the eastern U.S. has been described in Cincinnati (Ohio) in a child who had never left this state (Linnemann et al., 1978).

3.3.5. South and Central American TBRF

*B. venezuelensis* is essentially a human parasite giving a severe RF and is transmitted by *O. venezuelensis* (= *O. rudis*) an anthropophilic tick (and perhaps *O. talaje*). It occurs in Panama, Colombia, Venezuela, Ecuador, Paraguay. Other borreliae are transmitted by *O. talaje* (*B. mazzottii* and other unnamed borreliae), while *B. dugesii* is transmitted by *O. dugesii*, but the situation is not at all clear and further investigations are necessary to unravel the problem of TBRF in South and Central America (Felsenfeld, 1971; Rodhain, 1976).

3.4. Distribution in humans

Southern & Sanford in their review (1969) give a female predominance for LBRF (60 per cent) and a male predominance for TBRF (60 per cent). The distribution by sex is in fact most probably related to the type of population affected and by the occupational character of the disease in some areas, and not to any sex preference of the disease. For instance a male predominance of TBRF in Jordan is explained by the fact that shepherds are particularly exposed (de Zulueta et al., 1971). In Rwanda an adult female predominance is found in TBRF patients, which probably reflects the severity of the disease during pregnancy (Goubau & Munyangeyo, 1983a) (table 2). But no difference in attack rate by sex was found in the Grand Canyon outbreak (Boyer et al., 1977).

In reports on LBRF in the Sudan and in Ethiopia, the patients are predominantly males, due to the fact that the illness affects a population of migrant workers, often without their family (Bryceson et al., 1970; Rijkels, 1971a, b; Salih et al., 1977). Abdalla (1969) in his study of contacts of LBRF patients found 4.4 per cent of 565 men infected and 5.2 per cent of 328 women. In a pandemic the male:female ratio is 1:1 (Bryceson et al., 1970).

The age distribution of LBRF during epidemics depends largely on the age composition of the affected population. In the group of LBRF patients studied by Bryceson et al. (1970) in Addis-Abeba, 55/62 were aged between 10 and 29.

In TBRF the majority of cases is less than 20 years old (Southern & Sanford, 1969). The age distribution of *B. duttonii* RF cases in a health centre in Rwanda is given in table 2. Although children form the majority, all ages are affected.
TABLE 2
Distribution of *B. duttonii* Infections by age and sex at the Zaza Health Centre - Rwanda* (1,000 successive patients)

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 y</td>
<td>54</td>
<td>53</td>
<td>107</td>
</tr>
<tr>
<td>1 - 5 y</td>
<td>97</td>
<td>101</td>
<td>198</td>
</tr>
<tr>
<td>5 - 14 y</td>
<td>147</td>
<td>143</td>
<td>290</td>
</tr>
<tr>
<td>&gt; 14 y</td>
<td>159</td>
<td>246</td>
<td>405</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>457</strong></td>
<td><strong>543</strong></td>
<td><strong>1,000</strong></td>
</tr>
</tbody>
</table>

* E. de Pierpont, personal communication.

3.5. *Case fatality rates*

Case fatality rates tend to be higher in LBRF than in TBRF. In LBRF, case fatality rates vary widely: the highest rates are recorded at the height of epidemics (up to 40 and even 80 per cent in untreated cases) (Bayoumi, 1979), but vary from one outbreak to another, and tend to be lower at the end of an epidemic and in endemic circumstances. With treatment case fatality rates in LBRF can be kept around 5 per cent (Bryceson *et al.*, 1970).

In TBRF, case fatality rates differ from one geographical complex to another varying from 0 to 8 per cent. Mortality is higher in small children (Southern & Sanford, 1969) and pregnant women (Goubau & Munyangyeo, 1983a).

4. **Immunology**

4.1. *Serological tests*

Among the many serological tests that have been developed, the borreliolysin test (complement dependent) and the immobilizin test have been mostly used and are strain and relapse variant specific (Burgdorfer, 1976b). Disadvantages are the many cross-reactions between borreliae, the false positive reactions, the fact that the highest observed titre is not always that against the causative strain and the necessity to keep live borreliae in the laboratory (Felsenfeld & Wolf, 1974b).

Two newer tests, the indirect immunoenzyme test and the indirect immunofluorescence test, are performed on smears of borreliae, obviating the need to keep live borreliae, and are comparable in sensitivity and specificity to the immobilizin test (Felsenfeld & Wolf, 1974a, b; Burgdorfer, 1976b).

A direct immunofluorescence test with specific antisera showed a high specificity, allowing the differentiation of variants of *B. hermsii* in a mixed population (Stoenner *et al.*, 1982).

At present the serological tests for borreliosis have a limited interest for diagnosis, but are essentially used for research purposes.
4.2. Host response to infection

Studies of experimental infection of monkeys with *B. hermsii* and *B. turicatae* show an early immunological response to infection during the first week with an increase of immunocytes and production of IgM in spleen and lymphnodes (Felsenfeld *et al.*, 1970). There is an early rise in circulating IgM with low affinity, followed by mounting IgG levels with high affinity. Slowing down of IgM manufacturing occurs around day 35 and after 60 days only IgG remain elevated (Felsenfeld & Wolf, 1969). During the course of the illness antibodies appear in successive waves following each relapse and these successive antibodies are specific for the relapse variant of the borrelia (Felsenfeld & Wolf, 1969). IgA does not seem to play a significant role in RF (Felsenfeld & Wolf, 1975). Antibodies are found in the cerebrospinal fluid of infected monkeys, indicating probable central nervous system (CNS) involvement, even in infections where no glia cell reaction is observed as with *B. turicatae* (Felsenfeld, 1976).

Antibody titers in man may remain elevated for 6 to 9 months after the beginning of the disease (Felsenfeld & Wolf, 1974b). Immunity against reinfection with the same borrelia strain lasts six months to three years but for a shorter period in treated man and animals (Felsenfeld, 1976). Some protection exists in people who are under continuous challenge, for it is known that in highly endemic areas, natives tend to have milder disease than do newcomers. No data are available about hereditary immunity.

There are two opinions concerning the mechanisms of elimination of borreliae from de circulation (Newman & Johnson, 1981). One contends that antibodies play a major role, provoking lysis in the presence of complement. This can be observed in vitro and forms the basis of the borrelia liolsyn test. This view is supported by the fact that some studies found an activation of the complement system during RF (Galloway *et al.*, 1977), but other workers could not detect a complement depletion (Warrell *et al.*, 1983).

The other opinion is that phagocytosis is the more important mechanism. Newman & Johnson (1981) indeed concluded from studies with C5 deficient mice that an intact lytic complement pathway is not necessary for successful removal of circulating *B. turicatae*. They also observed that C3, whose cleavage products can serve as opsonins, is present on the surface of borreliae as early as two days before their elimination from mouse blood.

Butler *et al.* (1980) showed that phagocytosis of intact borreliae (*B. recurrentis*) by polymorphonuclear leukocytes (PMNL) occurs in vitro and in vivo. This phagocytosis is enhanced by antibiotic treatment (tetracycline, penicillin or erythromycin). Even in the presence of antibiotics the extracellular borreliae exhibit no signs of lysis of fragmentation and show an active pattern of normal rotational motility at the moment of enhanced phagocytosis. Bryceson *et al.* (1970) had already noted previously that antibiotics act too fast to be simply bacteriostatic. In vitro experiments with *B. hermsii* by Spagnuolo *et al.* (1982) suggest a role for immunoglobulins and possibly of the alternative complement pathway in the opsonisation of spirochaetes for phagocytosis by PMNLs.

Phagocytosis has been shown to occur in vitro also in monocytes, but on a much lower level (Butler *et al.*, 1982).
It is known since long that during successive relapses of the illness, strains of borreliae are found with different antigens: this is called «antigenic phase variation». In the past many studies have been performed to elucidate this phenomenon, often with conflicting results. Some found that serologic groups appear in a fixed sequence, while others found that the sequence of occurrence was not always the same. The number of variants originating in one infection varies from one author to another, as well as the methods that were used. It seems difficult to arrive to a clear understanding of phase variation by studies on natural infections, because the wide diversity of serological responses and cross-reactions does not allow a clear interpretation (Dodge, 1973b). Shuhardt and Wilkerson (cited by Southern & Sanfold, 1969) infected rats with a single spirochaete and found that the tendency for relapse was the same as with natural infection. Antigenic variation is thus a true characteristic of borreliae and not due to infection with a mixed population. They could also demonstrate both progressive and reverse antigenic variation (return to an earlier form).

Stoenner et al. (1982) succeeded in establishing cloned populations of different variants of B. hermsii in mice and to develop variant specific antibodies. They identified 24 serotypes arising from a single borrelia and then discontinued their search. They observed that relapse populations are not homogeneous but contain different serotypes. The first antigenic change is associated with clearance of the original population from the blood and is not related to the occurrence of relapse. In Kelly’s culture medium all serotypes of B. hermsii loose their characteristic surface antigen and all express the same «culture type» (C type). Reversal to the original serotype occurs after 2 to 3 mouse passages. In «fortified» Kelly’s medium borreliae express their surface antigens. Variants originating in this medium are roughly comparable to those originating from the same strain in mice: this is proof of spontaneous conversion, independent of antibodies. This is further confirmed by the fact that suppression of antibody with cyclophosphamide does not affect the occurrence of variants in mice. The same observation has also been made by Wright (1979) with B. duttonii. The role of antibody could be one of selection of variants and destruction of the dominant serotype populations. Although antibodies are not necessary to initiate conversion, other host factors may be involved as the occurrence of variants is not the same in mice and in rats.

Some progress has been made to elucidate the nature of borrelian antigens. Felsenfeld (1976) detected a common generic antigen in borreliae and at least two more specific factors. One of them, containing a polysaccharide, yields different degradation products during phase variations. The fact that formalin alters the antigenicity of borreliae suggests that proteins must be part of the antigens that characterize each serotype. Barbour et al. (1982a; 1983) working on 4 variants from the progeny of a single B. hermsii organism, isolated two major proteins pl and pII from whole cell lysates. While pII is a common antigen of all studied variants, with identical molecular weight and peptide pattern, pl can only be labeled with homologous serotype specific monoclonal antibodies. The pl proteins have a variable molecular weight and have little if any aminoacid sequence
homology among them as evidenced by peptide mapping. The C type has a pl (plc) with a much lower molecular weight than the other serotypes, but the difference in peptide pattern and the lack of cross-reactivity of plc specific antibodies with other pl molecules, pleads against it being the constant region of pl. pl is a surface protein with more accessible labeling sites than pil. Proteins with similar electrophoretic mobility as plc are also seen in in vitro parasaged B. turicatae and B. parkeri.

Another interesting point of borreliae is their cross-reactivity with Trypanosoma species, another organism with phase variation. The cross-protection against Trypanosoma has been used as a means of identification. Thus B. duttonii and the crocidurae group protect against T. brucei and possibly against T. gambiense, while B. hispanica and B. persica afford no such protection (Felsenfeld, 1971; Rodhain, 1976). Felsenfeld & Wolf (1973) showed that B. turicatae protects mice against T. cruzi but that this reaction is not entirely reciprocal, for whole extracts and antigenic fractions of B. turicatae are more active against T. cruzi than vice versa. It would be interesting to check the specificity of serological tests for trypanosomiasis in areas where RF is endemic.

5. Clinical picture, physiopathology and pathogenesis

5.1. Preliminary remarks

Relapsing fever has a variable presentation and although the same complaints and clinical signs can occur in any case, the frequency of occurrence varies enormously from one description to another. The illness is usually more aggressive in LBRF than in TBRF, but even in TBRF it varies from a subclinical infection to an illness with frequent complications, according to the geographical area, the strain involved and the immunity of the population. LBRF has also a varying severity from one outbreak to another. Mean incidence figures of the different symptoms by grouping large series of patients from the literature have therefore only limited interest because it does not correspond to the reality of a given situation.

Another important point is that there are no pathognomonic signs, except for the relapsing character of the illness, and that therefore many cases go undiagnosed even in endemic areas.

5.2. General evolution

Infection is followed by an incubation period of variable length, depending to some extent upon the infecting dose (Bryceson et al., 1970), varying from 3 to 18 days and sometimes more in TBRF. In LBRF an incubation of 4 to 14 days is reported but it is of course difficult to state the moment of infection as the affected person is in permanent contact with lice. The initial attack starts with the sudden onset of shaking chills with a rapidly rising temperature. The fever is most often remittent, occasionally intermittent and rarely continuous. The patient often complains of headache, backache, muscle pain, arthralgia and abdominal pain.
Other complaints include nausea, sometimes with vomiting, cough, dizziness and epistaxis. The clinical examination can be normal or reveal, among the most frequent signs, tachycardia, tachypnoea, jaundice, purpura, tenderness over the liver and the spleen with or without hepatosplenomegaly, an erythematous rash, meningismus. Often there is some alteration in sensorium, mostly lethargy, but sometimes delirium and agitation. The initial attack averages 3 days (12 hours to 17 days) in TBRF and 5.5 days in LBRF (4 to 10 days) and terminates with a crisis (see 5.6.). This is followed by an apyrexial interval that varies from 1 to 63 days (mean 6.8) in TBRF and 3 to 27 days (mean 9.25) in LBRF. This period is afebrile but often not asymptomatic, with persisting malaise or with the same symptoms as before the crisis but less intense. After this the patient may experience one or more relapses if untreated, the number of relapses being generally higher in TBRF (up to 13) than in LBRF (1 to 3). Each successive relapse tends to be of decreasing length and magnitude, although in some cases of TBRF it has been observed that successive paroxysms can become more severe (Thompson et al., 1969). A progressive decline of the general condition, with sometimes extreme weakness and weight loss can occur if successive relapses occur without adequate treatment (Goodman et al., 1969).

5.3. Jaundice

Jaundice occurs more frequently in LBFR than in TBRF. The rise in serum bilirubin is of hepatic origin with a rise of both fractions. A persistently high bilirubin is seen as an ominous sign. Liver damage is also reflected by raised transaminases, while the alcaline phosphatase is only slightly raised even in severely jaundiced patients (Bryceson et al., 1970). Hepatic involvement is further manifested by a tenderness over the liver, with or without hepatomegaly.

5.4. Bleeding

Purpura and epistaxis are the most common signs of abnormal bleeding in patients with RF. Purpura varies from a petechial rash to extensive ecchymoses and develops early in the first attack, never appearing during relapses (Bryceson et al., 1970). Petechiae are preferentially located on the trunk (Butler et al., 1979). A petechial rash does not affect the prognosis (Bryceson et al., 1970). Only mild epistaxis is seen in the beginning of the illness, but later in the first attack severe and prolonged epistaxis can develop. Bryceson et al. (1970) confirmed earlier experience that epistaxis in LBFR can develop after the crisis when spirochaetes can no more be found in the circulation. This was also our experience with B. duttonii infections. In cases of epistaxis the nasal mucosa appears hyperaemic with diffuse oozing of blood (Perine et al., 1974). Other haemorrhagic phenomena include haemoptysis, haematemesis, bloody diarrhoea, haematuria, subarachnoid and cerebral haemorrhages, splenic rupture, retinal haemorrhages. Bleeding is more frequent in LBFR than in TBRF, but again there are certainly differences between different foci. Karimi et al. (1976) have described a focus of an illness in Iran with bleeding as the major
symptom. From the blood of one patient a new *Borrelia, B. balthazardi*, was isolated (Karimi et al., 1979). These patients present with, in order of frequency, purpura, epistaxis, bleeding gums, haematuria, haematemesis, conjunctival haemorrhages and in some case haemorrhagic bullae in mouth and pharynx.

From the present knowledge petechiae seem to be due to thrombocytopenia, with perhaps also a direct effect of the numerous spirochaetes on endothelial competence and platelet dysfunction (Butler et al., 1979). In LBREF thrombocytopenia is indeed the rule with lower mean values in bleeding than in non-bleeding patients (Perine et al., 1971a). This thrombocytopenia is not due to a diminished production or to pooling in the spleen, for the marrow shows a normal megakaryocytosis and platelet numbers are not related to the size of the spleen (Perine et al., 1971a; Ahmed et al., 1980). Peripheral utilization due to vasodilatation and endothelial damage by spirochaetes, or removal with spirochaetes entangled with blood cells, is a possibility (Ahmed et al., 1980).

The possible role of coagulation defects in other haemorrhagic phenomena is not at present established. Prothrombin time (PT) and partial thromboplastin time (PTT) are prolonged to a variable extent in a number of patients. Often a decrease in factor V (to a moderate extent) and of Hageman factor is observed, while factor VII and X are normal (Perine et al., 1971a; Galloway et al., 1977; Ahmed et al., 1980). But Perine et al. (1971a) did not find a significant difference between the PT of bleeding and of non-bleeding patients. Apart from some cases, probably exceptional, who develop hypofibrinogenemia, the role of a certain degree of disseminated intravascular clotting in the consumption of coagulation factors and platelets remains controversial (Perine et al., 1971b; Dennis et al., 1976; Ahmed et al., 1980). In a number of cases elevated levels of fibrin degradation products can be found, increasing during the crisis (even with heparin treatment), but fibrinogen levels are usually normal or elevated. Butler et al. (1982) showed that thromboplastin is liberated by monocytes exposed in vitro to borreliae. This mechanism could trigger intravascular clotting.

In the different studies on bleeding in RF no distinction is made between patients with petechiae and patients with more important bleeding and in some studies there is no control group of non-bleeding patients. Could this not account for the difficulties in drawing clear conclusions?

5.5. Other complications

Neurological manifestations have been reported in RF. They are almost always reversible. Symptoms can precede or coincide, but often follow the febrile period (Olchovsky et al., 1982). They include signs of meningitis, with or without abnormalities of the cerebrospinal fluid, focal deficits, hemiplegia, paraplegia, Jacksonian epilepsy, paresthesias, neurologic pains, pupillary abnormalities and abnormal reflexes (unilateral Babinski’s sign). A severe psychic depression may persist for months (Southern & Sanford, 1969). In their review Southern & Sanford (1969) give a 30 per cent central nervous system (CNS) involvement in LBREF and 8-9 per cent in TBF. Bryceson et al. (1971) in a study of 62 LBREF patients found 2 patients
with ptosis and one each with dysphasia, delirium and coma (together 6 per cent), and a review of 209 infections by *B. persica* in Israel revealed 8 cases with CNS involvement (4 per cent) (Olchovsky et al., 1982). In my experience in Rwanda, signs of meningitis are often seen in TBRF and sometimes a psychotic behaviour with delirium and hallucinations follows the crisis and may persist for several days. Focal neural deficits are rarely if ever encountered in this RF focus, but this observation could be biased by the fact that these symptoms usually bring the patient to the traditional healer.

Ocular complications are described in some series, including uveitis and iridocyclitis (up to 15 per cent with *B. duttonii* in East Africa), retinal haemorrhages, retrobulbar neuritis and in some case residual defects and blindness (Southern & Sanford, 1969; Bryceson et al., 1970, Janssens, 1983). In Rwanda conjunctival hyperaemia is often seen, but iridocyclitis and visual disturbances in RF must be rare.

Further psychiatric, neurological and ophtalmological studies would be useful to clarify the clinical presentation and the pathogenesis of these complications.

Frequently patients complain of cough and chest pain and in some cases there are auscultatory signs. Sometimes bronchopneumonia or lobar pneumonia develops, probably due to superinfection.

Tropical thrombophlebitis has been attributed to RF (Gear, 1975).

During pregnancy the borreial infection is particularly intense and often provokes an abortion or a premature birth (Goubau & Munyangeyo, 1983a). In LBRF figures as high as 93 per cent of interrupted pregnancies have been given (El Ramly, cited by Bryceson et al., 1970). In the study of Bryceson et al. (1970), there were 2 abortions and one premature birth among 6 pregnant women. In *B. duttonii* RF a risk of 33 per cent of interruption of pregnancy is found, with a perinatal maternal mortality of 16 per cent (Goubau & Munyangeyo, 1983a).

Congenital borreliosis has been demonstrated in five cases of TBRF (Correa et al., 1964; Fuchs & Oyama, 1969; Steenbarger, 1982; Shirts et al., 1983; Goubau & Munyangeyo, 1983b) and was fatal in two of these cases, while two others were delivered for foetal distress. Remarkably, in the 2 cases born by caesarean section, the mother had been treated and apparently cured (without diagnosis) one month previously with erythromycin or erythromycin and cefamandole. Congenital RF is most probably underdiagnosed.

5.6. *The crisis and the Jarisch-Herxheimer reaction*

5.6.1. *General aspects*

An attack of RF terminates with a crisis in a number of cases. The same events occur after antibiotic treatment and represent a Jarisch-Herxheimer reaction (JHR) similar to the one originally described in syphilis. The reaction is more severe and develops faster in RF than in syphilis. The differences of the JHR in the 2 diseases may result from a different distribution of the spirochaetes (Warrell et al., 1971).

The frequency and the severity of the JHR varies with the antibiotic used and the causative organism. With the tetracyclines nearly all the
patients with LBFR experience a JHR (Knaack et al., 1972; Perine et al., 1974; Butler et al., 1978), while this is more variable with TBRF, with for instance 61 out of 104 patients (59 per cent) with *B. duttonii* infection experiencing a typical JHR (de Pierpont et al., 1983), while no JHR was observed in 23 patients with *B. crocidurae* RF (Aubry et al., 1983). The JHR of LBFR has been extensively studied.

5.6.2. Clinical description

The typical reaction starts about one hour after treatment with sudden rigors and a brisk rise in temperature. During this «chill phase», which lasts 10 to 30 minutes, the patient feels cold, there is no sweating, the respiratory and pulse rates as well as the blood pressure rise. At the end of the rigor the patient suddenly feels hot while the rectal temperature continues to rise, reaching a maximum about 2-3 hours after treatment. Around the time of maximum temperature, the spirochaetes disappear from the blood after clumping together. At the beginning of the «flush phase», the blood pressure falls and a profuse sweat breaks out. After this the temperature falls progressively, while the patient feels more comfortable. During the reaction cardiovascular collaps with death is possible (Bryceson et al., 1970; Bryceson, 1976).

5.6.3. Cardiorespiratory changes

The cardiorespiratory changes during the JHR have been studied in detail by Warrell et al. (1970). During the chill phase the metabolic rate, pulmonary ventilation, heart rate and cardiac output increase. Peripheral vasoconstriction, demonstrated by finger heat elimination (Bryceson et al., 1972), together with the high cardiac output explain the raised arterial pressure. Despite alveolar hyperventilation, arterial oxygenation is inadequate, probably reflecting a limitation of pulmonary oxygen diffusion. The high cardiac output and hyperventilation are in excess of metabolic requirements and cannot be explained simply by hyperthermia, hypoxia or acidosis, suggesting a direct effect of some toxic product. During the flush phase arterial pressure falls and remains low for many hours due to reduced vascular resistance. Small increases of glucose, lactate and pyruvate occur which can be prevented by inhaling oxygen.

During the JHR, cardiac abnormalities may appear or be accentuated, reflecting myocardial damage. The most frequent electrocardiographic sign is a prolonged QTc interval (Parry et al., 1970; Wengrower et al., 1984). In some cases ectopic ventricular beats are seen. Clinical signs of myocardial damage include gallop sounds, an increased central venous pressure, often returning to normal with digoxin, electrocardiographic signs of cor pulmonale and in some cases pulmonary oedema. The cardiac abnormalities associated with the very low vascular resistance and the high cardiac output may provoke cardiovascular collapse and death during the hours and days that follow the treatment reaction. At necropsy interstitial myocarditis is a common finding (Parry et al., 1970).

5.6.4. Haematological changes

Before the rigor the leukocyte count in the peripheral blood starts to fall sharply. The lowest point comes two hours after treatment at about the time spirochaetes disappear. After remaining at its lowest level for 30
minutes the leukocyte count rises progressively to above its original level. Mainly PMNLs disappear, but the lymphocyte count falls too. Vacuoles appear in the cytoplasm of PMNLs while they degranulate. The fall in PMNL count is not associated with any significant rise of serum muramidase, suggesting a transient sequestration rather than a large-scale destruction of the cells (Schofield et al., 1968; Bryceson, 1976).

During the JHR there is often a decrease of platelet count and an increase of fibrin degradation products (Dennis et al., 1976; Perine et al., 1971b).

5.6.5. Pathogenesis of the JHR

A first fact is a diminished concentration of Hageman factor and of prekallikrein during the JHR. Activation of Hageman factor initiates coagulation, but also activates prekallikrein to kallikrein, which in turn gives rise to vasoactive kinins.

Some circulating factor certainly plays a role in the development of the JHR, as reinfusion of onset-of-the-reaction blood gives a repeated reaction in some patients and plasma is pyrogenic to rabbits (Bryceson et al., 1972). The drop of the leukocyte count associated with the crisis, reaching its lowest level as the spirochaetes disappear (Bryceson, 1976) and the increased rate of phagocytosis corresponding to the onset of the JHR (Butler et al., 1980) suggested a role for a leukocytic pyrogen, liberated when the PMNLs degranulate. In fact, in vitro experiments showed that monocytes, not PMNLs, release a heat-labile pyrogen when exposed to B. hermsii organisms. This release of pyrogen does not need phagocytosis and is suppressed by inhibition of protein synthesis. The stimulation of mononuclear leukocytes to produce pyrogen could be due to some borrelial product (Butler et al., 1982).

Some arguments have been advanced indicating the possibility of an endotoxin (Bryceson et al., 1972; Bryceson, 1976; Galloway et al., 1977; Wright, 1980) but several facts cast serious doubts on the existence of such an endotoxin. The typical «cold-shock» of Gram-negative septicaemia is not seen in RF (Bryceson, 1976). The high frequency of asymptomatic persons with spirochaetemia and the low death rates in RF plead against endotoxin (Butler et al., 1979). The detection by the limulus test of endotoxin in the serum from patients who experience a JHR gives variable results (Galloway et al., 1977; Bryceson, 1976; Butler et al., 1979); it has therefore been proposed that the endotoxin, detected by the limulus test, originates from concomitant bacterial infections or from intestinal bacteria, penetrating the gut wall, anoxic from prolonged splanchnic pooling (Bryceson, 1976; Butler et al., 1979). No localized Schwartzmann reaction is elicited in rabbits by B. duttonii or B. recurrentis extracts (Wright, 1980; Butler et al., 1979). In contrast to the findings of Wright with B. duttonii (1980), other workers (Butler et al., 1979, 1982; Hardy & Levin, 1983) found that preparations of B. recurrentis, B. hermsii and B. hispanica produce a negative limulus test and no endotoxin can be detected in B. recurrentis by gas-liquid chromatography (Perine, P. L., unpublished observation cited by Warrell et al., 1983). Furthermore no increase of circulating endotoxin can be demonstrated in rabbits at the time when spirochaetes are killed (Bryceson, 1976).
While the existence of a borrelial endotoxin seems unlikely, borreliae (at least *B. recurrentis*) most probably possess a heat-stable non-endotoxic particulate pyrogen: the sediment, but not the supernatant, of centrifuged sonicated *B. recurrentis* organisms is pyrogenic even after heating to 100 °C for 15 minutes. The fact that endotoxin refractory rabbits have no response to borreliae (live or killed) is not an argument against a non-endotoxic pyrogen because this refractory state is not specific (Butler *et al*., 1979). Barbour *et al.* (1982, b) believe that the membranous blebs which develop under the action of penicillin could be related to this particulate pyrogen (see 7.1.3.). The exact nature of this borrelial product and its relationship to the JHR still have to be elucidated. In the search for this product one should take into account that the JHR occurs with varying frequency in the different species.

It is unlikely that immune complexes precipitate the treatment reaction. Bryceson (1976) never observed clinical features of immune complex disease, such as arthritis, episcleritis, glomerulonephritis, or cutaneous vasculitis after the JHR. In their experiments with mice Wright (1980) and Wright and Woodrow (1980) could not find in the kidney vasculitic or glomerular lesions indicative of immune complex deposition, nor C3 deposition by immunofluorescence; furthermore antibody depletion with cyclophosphamide did not suppress the treatment reaction and complement deficient mice (C3 to C9) had the same clinical course. Although Warrell *et al.* (1983) found immune complexes in some of their patients (but without determining their specific nature) they believe it to be unlikely that immune complexes would play a role in the JHR, because they did not detect any complement depletion.

5.7. Causes of death

The most common cause of death in RF is cardiovascular collapse, occurring during or after the JHR as a result of myocarditis and the strain imposed on the heart during the reaction. Hepatic failure occurs in some cases (Judge *et al*., 1974). Disseminated intravascular coagulation may sometimes be a cause of death (Perine *et al*., 1971b). Massive infarction of the cerebral cortex, meningitis and intracerebral haemorrhage have been occasionally reported (reviewed by Judge *et al*., 1974). Exsanguination as a result of massive haemorrhage is sometimes seen, usually due to splenic rupture (Salih *et al*., 1977) and I remember a 12 year old Rwandese girl who arrived dying at hospital after massive epistaxis. Obstetrical complications can also play a role (Goubau & Munyangayi, 1983a).

6. Diagnosis

A diagnosis based on clinical signs only is difficult except for the patient who has already gone through several relapses. All febrile illnesses as well as illnesses with jaundice, skin rashes, haemorrhages or thrombocytopenia are part of the differential diagnosis. One must also remember that simultaneous occurrence of RF with malaria, typhoid, rickettsiosis or kala-azar is possible (Southern & Sanford, 1969; Bryceson *et al*., 1970).
Especially in areas with low endemicity or outside an endemic area, the
diagnosis will often be made by chance thanks to a skilful microscopist
(Gatlin, 1977). Owing to the large numbers of circulating borreliae, the
diagnosis is usually established by finding spirochaetes in the peripheral
blood by microscopic examination. RF spirochaetes have affinity for acid
dyes and stain readily with aniline dyes. A blood film stained by standard
haematological methods or a Giemsa stained thick drop are the usual
methods (Burgdorfer, 1976b). Felsenfeld (1971) recommended a Giemsa
stain or a Wright stain followed by 10 to 30 seconds in a 1 per cent crystal
violet solution. An initial blood smear examination is positive in about 70
per cent of cases (Southern & Sanford, 1969). Fluorescence microscopy
with an acridine-orange stain was shown to be much more sensitive than
ordinary staining methods (Sciotto et al., 1983). Borreliae can also be seen
in fresh preparations with phase contrast or darkfield microscopy, their
specific motility helping in detection. In some cases borreliae can be
found in urine (Linnemann et al., 1978), cerebrospinal fluid (Fuchs &
Oyama, 1969) or sputum (Bryceson et al., 1970).

In cases of scanty parasitaemia, animal inoculation or concentration
methods are useful. Animal inoculation is of course difficult to use rou-
tinely and is mostly used for species identification. Ginger & Katz (1970)
separated successfully borreliae from the blood on DEAE cellulose anion
exchanger with the method used for trypanosomes. The microhaematocrit
concentration method (Cavill & Goldsmid, 1972) seems easy and efficient
for the detection of blood borreliae (Goldsmid & Mahomed, 1972).

Spirochaetes can readily be found in tissue sections or in leukocytes
with silver impregnation methods (Felsenfeld, 1971, Butler et al., 1980).
The acridine-orange fluorescence microscopy has been used successfully
to demonstrate borreliae in the placenta (Steenbarger, 1982).

Specific serological tests have a limited value for diagnosis due to the
frequent false positive reactions, but a rising titer may help to establish
a retrospective diagnosis. Elevated titers to proteus OXK are often found
especially in LBRF (Southern & Sanford, 1969).

Other laboratory tests will reflect the disordered physiology (livercell
necrosis, bleeding, etc.).

7. Treatment

7.1. Antibiotics

Antibiotics form the cornerstone of the treatment of RF but their use
is often complicated by a JHR.

7.1.1. Duration of antibiotic treatment

Two day courses of tetracyclines (Rijkels, 1971a,b) and even single
dose treatments with tetracyclines (tetracycline HCl 250 mg I.V. or
500 mg P.O., doxycycline 100 mg P.O., minocycline 100 mg P.O.), peni-
cillin (600,000 U - 1,000,000 U), ampicillin (500 mg P.O.), erythromycin
(500 P.O.) or chloramphenicol (500 P.O.) are very effective in terminating
an attack of RF (Knaack et al., 1972; Perine et al., 1974; De Clercq et al.,
1975; Butler et al., 1978; de Pierpont et al., 1983; Perine & Teklu, 1983).
On the other hand Peru and Teklu (1983) observed that many patients with LBRF treated with a single dose of an antibiotic have another episode of fever 4 to 6 days after resolution of the JHR and believe that this could be a relapse with indetectable parasitaemia. Therefore the ideal treatment for a complete cure will last at least two days, but single dose regimens keep their value in circumstances where multiple dose treatments are difficult to implement.

7.1.2. Choice of antibiotic

Several antibiotics are effective in RF: tetracyclines, penicillin, ampicillin, erythromycin and chloramphenicol (Butler et al., 1978; Perine & Teklu, 1983). Cephaloridine was shown to be effective in experimental conditions (Lapierre et al., 1971). The tetracyclines and penicillin are the best studied antibiotics in RF. Penicillin clears the spirochaetemia more slowly than the tetracyclines but it was considered to be less stressful than the tetracyclines, causing a less severe JHR (Rijkels, 1971; Knaack et al., 1972; Butler et al., 1978; Salih & Mustafa, 1977). In fact Warrell et al. (1983) showed that although peak temperature, peak pulmonary ventilation and metabolic rate are lower in patients treated with slow-release penicillin, the circulatory changes are the same as with tetracycline and more prolonged. Therefore the tetracyclines are the drugs of first choice. A further advantage of the tetracyclines is their activity against typhus in areas where LBRF and typhus occur together (Perine et al., 1974). In small children erythromycin can be an alternative (Le, 1980). In pregnant women the best choice still has to be defined: the ideal drug should cure the mother, prevent abortion, prematurity and congenital infection, and be free of side effects to the foetus.

7.1.3. Mechanism of action

There are only few data on the mechanisms by which antibiotics act on borreliae. As mentioned earlier (4.2.) phagocytosis of borreliae is enhanced by treatment with penicillin, erythromycin or tetracyclines. This effect of tetracyclines is somewhat surprising because tetracyclines are known to have an inhibitory effect on phagocytosis and to have a ribosomal activity on bacteria (Butler et al., 1980). Barbour et al. (1982b) studied the action of penicillin on B. hermsii. They found a minimum inhibitory concentration of 0.4 nmol/ml and a minimum bactericidal concentration of 3.1 nmol/ml. The primary morphological changes under the influence of penicillin are the formation of spheroplast-like structures and an increased number of small membranous blebs which, as the authors believe, could be related to the particulate pyrogen of borreliae.

7.2. Supportive treatment

The major problem to cope with is the JHR and its cardiovascular effects. Pretreatment with paracetamol (acetaminophen) or hydrocortisone has no sufficient effect to justify the routine use of these drugs (Butler et al., 1978). Meptazinol, an opioid antagonist, was shown to diminish the JHR significantly in a placebo-controlled trial of naloxone and meptazinol
(Teklu et al., 1983), but further studies with larger groups would be useful to weigh out the final benefit (in terms of lower mortality) against the possible side effects of this treatment.

Cardiac failure and extracellular fluid depletion may jeopardize the maintainance of a high cardiac output and of tissue perfusion during the prolonged flush phase. Infusion of at least 2 litres of fluid during the first 12 hours will prevent severe hypotension in most cases. During the flush phase the patient should be monitored for signs of cardiac failure (rising central venous pressure and pulmonary oedema), which will be effectively treated with intravenous digoxin. Conventional approaches to the treatment of pulmonary oedema such as the use of potent diuretics or venesecction could prove disastrous because of the greatly increased vascular capacity. The patient should be nursed in bed for the first 24 hours following antibiotic treatment to avoid postural hypotension (Parry et al., 1970; Warrell et al., 1970; Warrell et al., 1983).

8. Pathology

Few results from necropsy have been published during the last 15 years and they mainly confirm previous findings (Judge et al., 1974d; Ahmed et al., 1980; Gillum, 1976). No biopsies have been studied except from the skin. Our knowledge is thus limited to the changes that occur in fatal cases. What happens in the other cases can only be guessed from animal studies and the clinical picture.

In many fatal cases numerous petechial haemorrhages are observed over most internal surfaces.

The most characteristic features of the disease are found in the spleen which is enlarged with scattered foci of necrosis, presenting as 2-10 mm irregularly shaped areas of gray tissue. These foci are frequently associated with a follicle, but are sometimes seen either without relation to follicles or merely adjacent to them. At the periphery of the lesion a tightly entangled mass of borreliae is seen appearing as bluish amorphous material with hematoxylineosin staining. Splenic infarcts, haemorrhages and splenic rupture can occur.

Confirming the clinical observations, scattered foci of necrosis are found in the mid-zonal regions of the liver and a common finding in the heart is a diffuse histiocytic interstitial myocarditis.

Marked congestion of the brain can occur with mild oedema and sometimes meningeal of cerebral haemorrhages. Meningitis is an occasional finding.

The adrenals are grossly normal.

Grivet monkeys show changes very similar to those observed in humans (Judge et al., 1974b). In these the extent of histological changes increased with increase in spirochaetemia. Monkeys sacrificed during spirochaetemia show the same picture of myocarditis, hepatitis and focal necrosis of the spleen as observed at necropsy in humans: the splenic lesions vary from small crescent-shaped infiltrates of PMNLs at the edge of many follicles to complete destruction of entire follicles. After the initial attack, increasing fibrosis develops leading in extreme cases to a small distorted spleen.
9. Prophylaxis and control

Control measures of RF are directed against the vectors. In circumstances favourable to the dissemination of LBRF (overcrowding, wars, refugee camps, ...) control of lice by promoting personal hygiene (available water) and systematic delousing with DDT or lindane powder is essential. During the first Sudanese epidemic of this century (1926-1931) vigorous measures with isolation and treatment of patients, delousing of affected villages and establishment of delousing posts on the roads, succeeded in slowing down the spread of the epidemic (Bayoumi, 1979). There is a need for an efficient surveillance system in countries where LBRF is endemic (W. H. O., 1970), as LBRF could give rise to new epidemics if circumstances become favourable.

Domestic TBRF will only be eradicated definitively by better housing, but in the developing world this will only be achieved with improved economic conditions. Meanwhile inhouse spraying is a feasible alternative. Insecticides effective against Ornithodoros ticks include benzene hexachloride (Gammexane®, BHC) 2 per cent, Aldrin® 1 per cent, diazinon 0.5 per cent, malathion 0.5 per cent, pyrethrum, paradichlorobenzene, polychlorides (Southern & Sanford, 1969) and isopropoxypatentethylcarbamate 1.1 per cent (Baygon®) (Boyer et al., 1977). It is noteworthy that in Central Africa TBRF was brought back to a very low level as a positive «side effect» of antimalaria campaigns by inhouse spraying, but that the lack of surveillance allowed a massive comeback of the illness 15 years later (Janssens, 1983). Using bedsteads and keeping domestic fowl away from the houses diminishes the proliferation of O. moubata. Karimi (1982) showed that Ornithodoros ticks can be cured of their borrelia carriage by letting them feed on guinea pigs treated with tetracycline 100 mg/kg. It would be interesting to know if therapeutic concentrations in humans have the same effect in ticks feeding upon them.

Non-domestic TBRF can be prevented by the use of repellents like diethyl-m-toluamide, by rodent proof construction of buildings used as seasonal shelters or removal of rodent nests and insecticide spraying of infested constructions (Boyer et al., 1977). Use of rodenticides instead of tick control serves only to exacerbate the problem by reducing available animal hosts (Edell et al., 1979). Wild foci of TBRF can be detected and treated in areas where new or temporary human settlements are considered (Adbullaev & Bauramova, 1970).

10. Perspectives and conclusions

It is clear that in the field of RF there are more questions than answers and that many of the facts have to be considered with caution as they are based on few studies and should be further confirmed. Further research is necessary in all the aspects of this disease, especially in fields directly relevant to the management of patients and to the control of the disease.

Work on RF has a wider interest than the impact on the illness itself. Borreliae are not the only organisms with phase variation and immunological studies on borreliae and trypanosomes could benefit one another.
The high number of circulating borreliae offers a unique opportunity to study phagocytosis of bacteria and the factors that influence it in vivo. The predictability of the events during the JHR makes it a model for the physiology of fever. Finally, the new culture methods for RF borreliae will also have an impact on our knowledge of other pathogenic spirochaetes (e.g. lyme disease spirochaetes).

Hopefully this paper will contribute to a revived interest for relapsing fevers and the questions they raise.

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