Journal of Spirochetal and Tick-borne Diseases

Volume 6 Summer 1999

REPRINT OF
BORRELIA: STRAINS, VECTORS, HUMAN AND ANIMAL BORRELIOSIS

Oscar Felsenfeld, MSc, MD

The Journal of the Lyme Disease Foundation

Journal of Spirochetal and Tick-borne Diseases

Journal of Spirochetal and Tick-borne Diseases

Volume 6 Summer 1999

13TH INTERNATIONAL SCIENTIFIC CONFERENCE ON LYME DISEASE & *OTHER* TICK-BORNE DISORDERS *EMPHASIS: PEDIATRICS & NEW RESEARCH*

MARCH 24 - 26, 2000

Hartford Marriott Farmington (CT, USA)

Poster Presenter Registration: $225 incl: 2 lunches, 4 breaks, hand-outs, poster dislpays, presentations, 2 receptions 6pm - midnight

Room $79 single/double **Receptions** 3/ 24 & 25 **Presentations** 3/25 & 26

Abstract for Oral & Poster Presentations

Deadline: Oral Submisions 12/2/99 Poster Submissions 2/25/00

Abstracts must be in English and you should use a separate form for each submission. All abstracts not chosen for oral presentation will be considered for poster presentation.
Choose a category from the list and check the corresponding box. Type your abstract within the area shown. Type the title in capital letters, list authors, affiliation and location where research was done, and use an asterisk to indicate the poster presenter. No additional pages are allowed.
Each abstract should contain: objectives of the research, methodology employed, result, and conclusion. A conference committee member will contact you regarding more information, as needed. Accepted abstracts will be published in the Conference Program Book, which will be distributed to all conference registrants. Accepted abstracts are printed as submitted by the authors.

DISEASE _____

PREVENTION & BASIC SCIENCE
- __ **Ecology, Entomology**
- __ **Vaccine**
- __ **Animal models**
- __ **Microbiology**
- __ **Pathogenesis**
- __ **Pathology**
- __ **Other:**

PATIENT MANAGEMENT
- __ **Clinical manifestations**
- __ **Laboratory diagnosis**
- __ **Early disease management**
- __ **Late disease management**
- __ **Chronic disease management**
- __ **Other:**

Name_____ phone_____
Title_____ fax _____
Affiliation_____ e-mail _____
Street_____
City_____ State_____ Zip_____ Country_____

Return to: Lyme Disease Foundation, One Financial Plaza, Hartford, CT 06103-2610
860-525-2000 fax: 860-525-8425 e-mail: Lymefnd@aol.com web: www.Lyme.org

Journal of Spirochetal and Tick-borne Diseases

The *Journal of Spirochetal and Tick-borne Diseases* (ISSN:1060-0051) (GST#129780466) is published quarterly by SLACK Incorporated, 6900 Grove Road, Thorofare, New Jersey 08086. Dates of publication are: March, June, September, and December, on the third week of the publication month.

Subscription Rates: Physician: $75.00/yr; Institution: $95.00/yr; Single copies: $25.00; Students, fellows, and residents: $45.00/yr; Foreign: add $20.00 for postage ($10.00 for Canada). **To receive student/resident rate,** orders must be accompanied by name of affiliated institution, data of term, and signature of program/residency coordinator on institution letterhead. Orders will be billed at single rate until proof of status is received. **Back issues** can be ordered at a cost of $25.00 per issue. Back issues sold in conjunction with a subscription are on a prorated basis. Requests for orders should be sent to the *Journal of Spirochetal and Tick-borne Diseases*, SLACK Incorporated, 6900 Grove Road, Thorofare, New Jersey 08086.
Change of address notices, including both the old and new addresses of the subscriber, should be sent at least 1 month in advance of effective date. Include old and new addresses and label from recent issue. The publisher cannot accept responsibility for undelivered copies.
Postmaster: Send change of address to: *Journal of Spirochetal and Tick-borne Diseases*, SLACK Incorporated, 6900 Grove Road, Thorofare, NJ 08086. Third class postage paid at Thorofare, NJ 08086. **Back issues** can be ordered at a cost of $25.00 per issue. Back issues sold in conjunction with a subscription are on a prorated basis. Requests for orders should be sent to the *Journal of Spirochetal and Tick-borne Diseases, SLACK Incorporated, 6900 Grove Road, Thorofare, New Jersey 08086.*

Editorial content: Topics relating to understanding disease mechanisms and the application of better diagnostic techniques and treatment strategies for all individuals suffering from spirochetal and tick-borne diseases. ***Letters* to the Editor** in the form of correspondence related to material published in the Journal or some aspects of spirochetal and tick-borne diseases may be submitted. Such letters, if related to work previously published in the journal, will be referred to the author of the original work for a response.

Publisher

For submissions and subscriptions
SLACK Incorporated
6900 Grove Rd.
Thorofare, NJ 08086
609-848-1000

Editorial Staff

Executive Editor
Kaye Coraluzzo

Assistant Managing Editor
Patricia Alexander-Smith

Editorial Assistant
Aileen Schneider

Advertising Sales

Publishing Director/Advertising
Wayne McCourt

Advertising Sales Representative
Kelly Wark

Publishing Group

Vice President/Group Publisher
Richard N. Roash

Publisher
John C. Carter

Editorial Director/Journals
Jennifer A. Kilpatrick

Circulation Manager
Lester J. Robeson, CCCP

Production Director
Christine Malin

Production Coordinator
Joanne Patterson

Business Manager

For correspondence
Karen Vanderhoof-Forschner
Lyme Disease Foundation
One Financial Plaza
Hartford, CT 06103-2610
Telephone: (860) 525-2000
Fax: (860) 525-8425
e-mail: lymefnd@aol.com
Internet: www.lyme.org

Warren Harold Green
1915-1992

GREEN, WARREN HAROLD, publisher; born Auburn, IL, July 25, 1915; s. John Anderson Logan and Clara Christina (Wortman) G.; married Joyce Reinerd, October 8, 1960; deceased June 6, 1992. Student, Presbyterian Theological Seminary, 1933-34, IL Wesleyan University, 1934-36; M.B., Southwestern Conservatory, Dallas, 1938; M.M. St. Louis Conservatory, 1940, PhD, 1942; H.L.D. (hon.) Southeastern University, New Orleans; L.L.D. (hon.) Institut de Droit Practique, Limoges, France, 1983; D.D. (hon.), California Theological Seminary, 1980; Litt.D. (hon.), Confederation Europeene de L'Ordre Judiciaire, France, 1983. Professor voice, composition, conducting and aural theory at St. Louis Conservatory, 1938-44; program director U.S.O., 1944-46; community service specialist Rotary International, Chicago, 1946-47; editor in chief Charles C. Thomas, Pub., Springfield, IL, 1947-66; publisher, president Warren H. Green, Inc., St. Louis, 1966-1992, Warren H. Green International, Inc., 1970-1992; managing director Publisher's Service Center, St. Louis, Chicago, and Longview, TX, 1967-92; vice president Epoch Press, St. Louis, 1986-92; cons. U.S., European publisher's professional societies; lecturer: medical publishing, Civil War. Contributed articles to professional journals, books on Civil War history, writing, editing. Recipient Presidential citation for outstanding contribution to export expansion program U.S., 1973, citation MD Crime Investigating Committee, 1962, citation International Preventive Medicine Foundation, 1977, citation AMA, 1978. Member Mayor's Committee on: Water Safety, Metropolitan St. Louis Art Museum, MO Botanical Gardens. Member: Civil War Round Table (v.p. 1969-1991), American Academy Criminology, American Academy Political and Social Science, American Association Medical Book Publishers, American Judicature Society, Great Plains Historical Society, St. Louis Philharmonic Society, MO Botanical Gardens, St. Louis Art Museum. Clubs: MO Athletic, Media, Elks, World Trade, Direct Marketing St. Louis.

"As God gives us the ability to seek the truth, know the truth, and be true to others as well as ourselves, and as God gives us the understanding to maintain a high sense of values in our work and in our relations with all fellow men, it naturally follows that attitudes, endeavor, love of people and all other living things, cause one to like and be liked, which is the first step towards any worthwhile goal."

CHAPTER I (cont'd from Vol 6, Spring)

HISTORY

Many historical accounts of relapsing fever are based on the studies of Scott.[634]

Epidemic relapsing fever was recorded and described by Hippocrates in Thasos as "ardent fever."[308,634] Bryceson et al[127] believe that the "yellow fever" experienced in Europe during the VIth century may have been relapsing fever. The five epidemics of "sweating sickness" that swept England between 1485 and 1551 included outbreaks of relapsing fever.[127,491] Louse-borne typhus also prevailed at that time and "famine fever" was the common designation of both infections. Gloucestershire was wiped out in the beginning of the 18th century by "famine fever." England and Ireland suffered from this disease also in the 17th and 18th centuries. The first well-documented epidemic of relapsing fever was described in Ireland between 1739 and 1741 when Rutty recorded its clinical features. The epidemic then spread from Ireland to Scotland and England. The outbreak in 1834 to 1848 in Edinburg was particularly severe. The designation "relapsing fever" was first used by Craigie in 1843.

The Scandinavian countries became infected in 1788 from Russian ships that made port in Sweden. The last epidemic in Germany occurred from 1867 to 1868, in Ireland from 1868 to 1871. Later, improving hygienic conditions kept the disease from West Europe.

Louse-borne relapsing fever was imported into the United States from England and in 1844 caused the famous Philadelphia epidemic. This infection persisted in the eastern region of the United States for about 30 years. In 1874, there was a similar outbreak among Chinese laborers in California.[193] Tick-borne relapsing fever was recognized soon after the West was settled.[727]

The causative agent of epidemic relapsing fever was discovered in 1868 by Obermeier who did not publish his paper on this subject, however, until 1873.[507] This organism is now designated as *Borrelia recurrentis.* In the past, it was called *Spirocheta obermeieri, Protomycetum recurrentis, Spirocheta recurrentis,* and other names.[128]

Little is known about louse-borne relapsing fever before the 18th century except that it prevailed in cold and poor countries where lice were common. It was known to have occurred in Africa and in China.[149,363,641]

Carlisle,[145] Geigy,[303] and others agree that Livingstone was the first to note in 1857 that tick-borne relapsing fever was present in Angola and Mozambique and that the disease was familiar to the local African and Portuguese inhabitants. Lamoureaux[430] reported that Drury had observed tick-borne relapsing fever during his trip to Madagascar in 1702 to 1720 but it remained for Cook[198] in Uganda to notice the presence of *Borrelia* in the blood. Ross and Milne[613] in the same area and simultaneously Dutton and Todd[250] in the Congoes, as well as Koch[417] in East Africa, confirmed these findings and demonstrated that tick-borne *Borrelia* may cause disease in monkeys and man. Both Dutton and Todd contracted the disease, and Dutton died of it.[303]

The "bilious typhoid" in Egypt, described by Griesinger in 1857[617] appears to have been relapsing fever, but Napoleon's surgeons were the first to diagnose relapsing fever correctly in that country.[395]

Among other investigations of historical importance are those of Koch[418] in East Africa which resulted in the naming of a *Borrelia* strain *Spirochaeta kochi;* the studies of Novy and Knapp[547] of the movement of *B recurrentis,* and their observation that antibodies begin to develop during the first attack of the disease; the review of Hindle[361] of relapsing fever in tropical Africa; the investigation of the mode of division of borreliae and a review of the *Borrelia* problem by Dobell[243]; the experiments of Ross[612] on patas monkeys with strains isolated in Uganda; the survey of the distribution of the vector *(Ornithodoros moubata)* of *B duttonii* in Africa by Nuttall,[548] the attempts of Nicolle et al[536] to transmit tick-borne borreliae to lice; the first demonstration of the infectiousness of the coxal fluid of *O moubata* by Todd[684]; and the study of the ecology of *O moubata* between 1892 to 1905 by Todd[685] which led him to predict that as travel increased, the tick, and with it also tick-borne relapsing fever, would spread further through Africa.

Relapsing fever has been observed in all parts of the world, except Australia, New Zealand, and Oceania, where only solitary imported cases have been seen.[363]

In Africa, reports of past occurrences are available from the former Gold Coast.[617,618] LeGac[439] described an epidemic in Oudaii (Chad) between 1925 and 1928. Hawkins[338] studied *B duttonii* infections in Tanganyika. Fendall and Grounds[269] believed the disease to be retreating in Kenya, where louse-borne relapsing fever was introduced by refugees from Abyssinia.[296] The Sudan had several louse-borne outbreaks. After the first World War, repatriates brought infected lice with them to that country. The ensuing epidemic stopped only at the forest.[439] Atkey[30] described this 1926 to 1928 outbreak. Kirk[411] believed that the constant population movement from and to Abyssinia steadily supplies the Sudan with infected lice. Hindle[365] observed that louse-borne relapsing fever swept over the major part of the northern part of Africa from 1925 to 1928.

Relapsing fever is not new to many parts of Africa. Kirk[411] noted the louse-borne relapsing fever was introduced into the Sudan from Egypt between 1908 and 1924, in 1926 from French West Africa, and during the

Abyssinian War in 1936 from Italian Africa.

Egypt suffered during the Napoleonic invasion (see above) and, according to Kamal et al,[395] experienced an outbreak that was recognized as relapsing fever by Sandwirth and Engel in 1884. The disease has been systematically studied since 1906 in that country.

Algeria, Tunisia, and Morocco have been recording louse-borne relapsing fever since 1903.[534,535,641,642] The 1907 to 1914 epidemic in Algeria offered an occasion for numerous scientific studies.

Somaliland, closely adjacent to the Abyssinian-Sudanese focus of relapsing fever, experienced tick-borne cases among troops in her formerly British territory.[244] Other occurrences of the disease were recorded by Italian authors.[610] Moise[497] commented on relapsing fever in Somaliland, pointing out that the most effective African tick vector, *O moubata*, is very scarce in that area. He suspected that there were other transmitting agents. A similar dispute arose in Madagascar, where Lamoureaux[430] recorded the appearance of the disease in military personnel who used the route between Morandava and Majuna in 1911 and 1912. Suldey[672] encountered tick-borne cases on the west coast of Madagascar in spite of the scarcity of a recognized vector.

In South Africa, relapsing fever remained undiagnosed until an outbreak was observed in the Cape Province among miners who had come from the North and had brought with them the tick *O moubata* as a good luck charm which then began to thrive in their huts.

In Yemen, in Asia Minor, Franchini[277] was unable to find ticks that were capable of conveying borreliae and concluded that the louse was the only vector.

During the first world war, Egypt was heavily hit by louse-borne relapsing fever.[395,670] In the four years between 1916 and 1920, 40,000 cases were recorded. Syria and Turkey also became infested.[628,734] Mesopotamia had an outbreak in 1918 among Turkish railroad workers.[519] During the aftermath of World War I, from February to August 1920, troops became infected in Birjand, East Persia. Relapsing fever in the absence of lice was reported in Jinnuk, East Persia,[337,739] while the areas of Sharifabad, Meshed, and Turbad had ticks as well as human lice that were able to carry borreliae.

In India, where Mackie was the first to state in 1907 that the human louse carried epidemic relapsing fever, numerous episodes of the disease were recorded. "Spirillar fever" was described in a group of Ghurka tea garden workers in Darjeeling.[392] Roy[614] reported an outbreak in the Seoni District (Upper Provinces) in 1919 to 1920. It was believed[206,207] that louse-borne relapsing fever was endemic in Agra and Oudh, and spread from there to other areas. Gill[316] published the statistics on the outbreaks in the Punjab in 1869, 1878, 1891, 1906, and 1920, which claimed 26,000 lives.

Browse[114] described tick-borne recurrent fever in Qetta, principally among military camp followers who were new to the area and who lacked immunity.

Cases were described in Afghanistan by Avanessov[33] who did not, however, find the vector.

China has been the home of louse-borne relapsing fever for a long time. Records in the western literature are available from West China,[387] Sechuan,[388] an outbreak in an orphanage in Peiping,[172] and a review of 337 cases treated in the Peiping University Medical College Hospital between 1921 and 1937.[176] Toyoda[687] studied *Borrelia* strains collected in Manchuria.

Indochina was infected from China. There were 373 cases in Hanoi during the first half of 1912.[508] The disease was found in Nghê-An.[357] Casoux[149] and Millous[495] described the course of relapsing fever that during the 1910 to 1911 cool period alone took about 500 lives in Annam. The disease spilled over into Thailand.[733] Further data are not available from that country.

As stated previously, louse-borne relapsing fever came from China to the United States in 1874.[494] Later, however, tick-borne relapsing fever was the type of the disease that prevailed on the Pacific Coast. A summary of such instances for the years 1921 to 1937 was presented by Wheeler.[737] Meador[489] reported 5 cases from Colorado. Bannister,[66] Hemingway et al,[356] and Thayer[680] rendered further reports from the Southwest and Northwest. Graham[321] described a case of a boy who entered a cave in Denton County, Texas, that has been known for years to harbor infested ticks, and became ill with relapsing fever. Kemp et al[408] surveyed the epidemiology in Texas. Closson[183] described it in Kansas. Briggs[111] and Coleman[193,194] reviewed the situation in California. Palmer and Crawford[560] reported an outbreak in British Columbia. The transmitting tick was not found in that episode in Canada.

Louse-borne relapsing fever was observed in Panama by Connor.[197] Tick-borne cases were seen in March and April, 1921, in hunters and in rats captured in the Arraiján area.[68] Dunn and Clark[248] studied animal hosts and vectors in Panama.

Relapsing fever was introduced to Ecuador probably from Colombia during the revolution in 1896.[443] It is now tick-borne in both countries.

Chiriboga[164] reported louse-borne infections from Peru. Prado[588,589] described the history of the disease in that country, dating back to population movements in the late 19th century.

During the Balkan War louse-borne relapsing fever was not common in Macedonia in spite of the presence of the vector. The disease was at home in the trenches of

World War I, principally in the countries of the Central Powers and in East Europe. An outbreak initiated by the distribution of Austrian prisoners of war in Serbia for work in the fields lasted 6 months.[377] Cantacuzène[143] noted that louse-borne relapsing fever was endemic in the eastern part (Besarabia) of Rumania but there was an upsurge of the disease and of epidemic typhus in 1916. Poland was heavily infested at that time. The city of Lodz alone had 343 cases between March and December, 1917.[473] Sterling-Okunewski[669] and Lipinski[453] reported additional instances in Poland and in Hungary. Oettinger and Helbreich[551] related the course of the disease on the Russian front.

The tick-borne form has been observed in the Caucasus since 1928 by Maruashvilli[475] and in Tashkent.[399] A thorough analysis of the natural foci of the disease in Turkemenia followed later by Petrishcheva.[571]

It appears that the association of man and louse that was considered a somewhat vexing event but not an evil part of life, until hygienic concepts began to prevail in the 19th and 20th centuries, has endowed the history of louse-borne relapsing fever with a continuity that has been interrupted by epidemic outbursts perhaps only at times when the immunity of larger population groups reached a low ebb, or when hitherto uninfected populations came into contact with infected groups of people.

Louse-borne relapsing fever spread during and after World War I over large areas of the Old World as a result of the propagation of lice among dislocated soldiers and civilians living under unhygienic conditions, who were compelled to move about from locale to locale. These epidemics gave impetus to the study of the disease. Most basic clinical and epidemiologic concepts of relapsing fever were elaborated during these periods. Further outbreaks, as well as less extensive epidemics, have also been studied thoroughly and will be analyzed in subsequent chapters. Among these belongs the recognition of the continuity and contiguity of louse-borne relapsing fever.

The study of tick-borne or endemic borreliosis went through the same phase as the rest of microbiology, when the major interest apparently was to discover new species and strains, Borreliosis is a dynamic condition, a cyclic disease characterized by a cyclic causative agent. No wonder that great numbers of species have been proposed on the basis of minor or not fully understood strain variations and mutations, incomplete knowledge of the vector, and epidemiologic observations that were not extended far enough "longitudinally" and "laterally." Some of the taxonomy both of *Borrelia* and *Ornithodoros* still has to be untangled, principally in Central Asia and South America. A further complication arises from the transliteration of the names of some authors, principally in the USSR, who had published in Russian and German, choosing the method of transcription of certain letters of the Cyrillic alphabet more or less arbitrarily. One encounters in the literature Pavlovsky, Pawlowski, Pavlovskii, Pavlovskyi; *B latishevyi, B latischeiwyi, B latishewyi,* and so forth. The reader is asked for his kind indulgence when encountering such discrepancies, principally in the references.

EPIDEMIOLOGY

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

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

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

Epidemic Relapsing Fever

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

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

Epidemic relapsing fever has no other known reservoir than man. Admittedly, the monkey louse may transmit the causative *Borrelia,* and laboratory experiments have substantiated that nonhuman primates are susceptible to the disease. To the knowledge of this author, naturally infected monkey or ape populations, however, have not yet been reported. Recollecting also that the human louse does not transmit the infection to its progeny and that it has to be mutilated or killed to infect the wound resulting from its bite with celomic fluid containing borreliae, it is obvious that one louse can infect only one person, and therefore an increasing array of *P humanus* is necessary to create an epidemic. Moreover, the infected lice must have a chance to gain access to a nonimmune person within their rather limited life span in order to transmit the infection. Such an opportunity arises when people are compelled to live in close proximity to one another.

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

The time for epidemics is the cold season (winter) when people huddle together, and heavy clothing is being worn, in which lice find a feasible microclimate. Accordingly, in hot and humid Central Africa the lightly dressed inhabitants escape lice. In Southern India, lice are found only among the very poor. Corkill[202] demonstrated that the time sequence of relapsing fever may be changed. The malady appeared in the spring in Gedaref, Sudan, being activated by kala azar infections. Baltazard et al[63] observed the reappearance of the disease by the end of the winter and considered the possibility that this might have been due to a variant *Borrelia* strain. Several authors[163,388,645,649] have corroborated the parallel between louse population and relapsing fever in China.

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

The seasonal occurrence of relapsing fever may be changed also by migration. Kirk[411] pointed out that migration between Egypt, Sudan, and the former French West Africa was accompanied by the introduction of infested lice. More will be given about this in the discussion of the epidemiology in Abyssinia. Chiao[163] observed also the spread of relapsing fever along highways in China, which resulted in about 5500 cases among people associated with wayside inns and farmers living along the routes. Lanzo and Tresca,[432] commenting on 2914 cases in the former Erythrea Colony, also saw a shift from the classic winter relapsing fever season to June through September because of the time of labor migration.

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

On the other hand, nonimmune immigrants entering infected areas, as in Abyssinia, principally seasonal laborers and job seekers who live under poor conditions, may acquire *Borrelia* infested lice, and the disease.

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

During wars and other disasters, such as earthquakes, famines, fires, and floods, people are often compelled to

flee in masses, and to live in congested quarters. Water is usually scarce, clothing is not properly washed, and conditions become favorable for the multiplication of lice. Then relapsing fever epidemics break out.

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

During this epidemic Stuart[670] observed that the disease was at first mild in Tunisia, Algeria, and Morocco, but later became severe with a 10% to 12% mortality. Gaud and Morgan[298] reported a 50% morbidity rate in 1942 to 1944. This was probably due to lack of herd immunity because relapsing fever was absent from that area for 25 years. Bryceson et al,[127] commenting on the 20-year periodicity of relapsing fever in Africa, remarked that this may be the time needed for a nonimmune population to grow up, or it may be caused by military activities recurring after two decades—in 1903, 1923, 1943.

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

Spanish Morocco was infected from the former French Morocco. Between March through July 1945, 168 cases were reported. To the East, Egypt was plagued simultaneously by louse-borne typhus and a relapsing fever epidemic. Halwani[333] and Kamal et al[395] stated that about 100 000 persons became ill. Gaud and Morgan[298] described the spread of the disease to Iran, Jordan, Syria, Aden, and Palestine, where only scattered instances were observed, while Iran and Kenya experienced true epidemics. There were 200 cases in Haifa.[332] The disease in Kenya was studied by Heisch.[340] The aftermaths of the introduction of relapsing fever from Seihut, South Arabia, to Mombasa, Kenya, by several dhows carrying patients who imported the disease, has been demonstrated by the observation of isolated cases by Ombati and Ojiambo.[553] Saglan[621] commented upon the mild outbreak in Turkey. The disease reached true epidemic proportions, however,

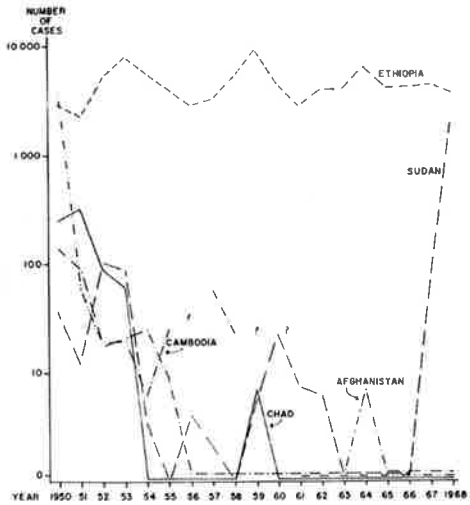


Figure 27. Distribution of louse-borne relapsing fever, 1950-1968, according to reports to W.H.O.

in Abadan, Iran, in November 1945 to June 1946, with 1087 cases, commencing after an unusual cold spell. This was the first extensive louse-borne relapsing fever epidemic recorded in Iran. Head lice were found on 88% of the patients, and *B recurrentis* was isolated from some of these ectoparasites. It is not certain that the small outbreak in Northeast Bengal, with 9 laborers becoming ill, was related to the large World War II epidemic.[152]

In Europe, Yugoslavia suffered both from louse-borne typhus and relapsing fever. Serstnev[644] believed that residual endemic foci may still exist in that country.

Romania had about 4000 cases according to Gaud et al[297] but Zaharia[744] saw 58 cases daily in 1945 and 1946 in a single hospital. Exact statistics are not available from Poland. Lipinski[453] reported a milder course of the disease than during World War I, with a 0.25% case fatality rate. He ascribed this to prompt treatment with arsenicals.

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

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

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

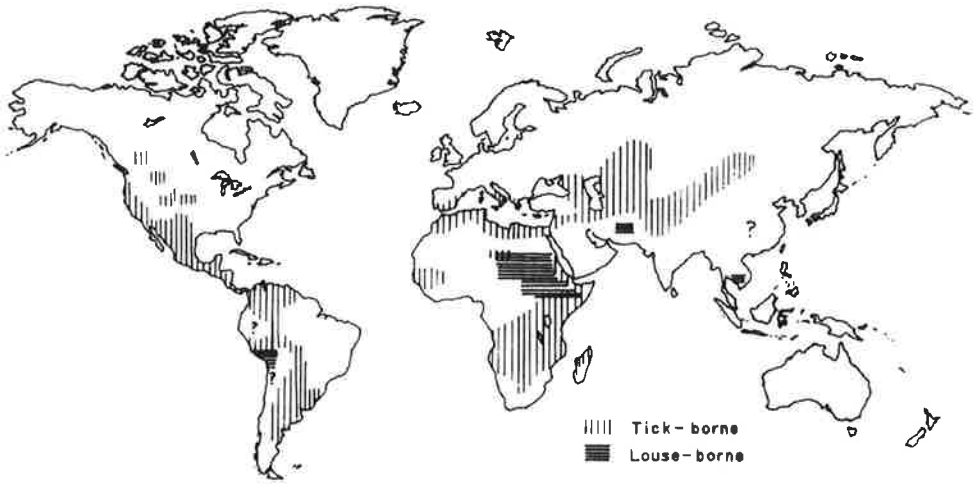


Figure 28. World distribution of relapsing fever, 1950-1969.

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

After the World War II epidemic subsided, Afghanistan reported 138 cases in 1958 and a few in 1964. Afghanistan is mountainous, dry, and cold. Such areas are favorable for relapsing fever. Unfortunately, few (or no) data are available from the Pamir, the Himalayas, and from many of the South American highlands. At the other extreme lies hot and wet Cambodia with 4216 reports in 1950. The number of cases decreased to 6 in 1954, and a few were reported in 1957 and 1958. Although no accounts are available from Mainland China and North Vietnam, it is possible that louse-borne borreliae are being imported from those countries to Cambodia. On the other hand, isolated foci in Cambodia may be residua of the epidemics during the first part of this century, perhaps brought in by migrant tribes or remaining active in isolated spots.

According to the reports reaching the World Health Organization,[20] Abyssinia had 2860 cases in 1950. The number of annually reported instances increased to 7499 in 1953 and 8760 in 1959, with a low of 2760 in 1961. The number increased to 5971 in 1964 and came to 3729 in 1968. All provinces are infected at present (1969 through 1970) and the number of reported cases has not been below 2760 in any year between 1950 and 1968.

The Sudan had less than 100 cases per year until 1953, then very few until 1967 when 70 instances were reported, and 1948 in 1968. This has to be considered a veritable epidemic. All five provinces of the Sudan are now infected.

Developments in the Chad followed the opposite path. A few hundred cases were reported in 1950 and 1951, less than 100 in 1952 and 1953, very few in 1959, then none. Figure 27 shows the fluctuations in the number of cases reported to the World Health Organization on a logarithmic scale. It has to be remembered that only louse-borne but not tick-borne cases are reportable according to the International Sanitary Regulations now in force.[379]

The great number of cases in Ethiopia and the Sudan deserve further attention.

Bryceson et al[127] pointed out that the Abyssinian highlands are cold, principally during the local winter (June through September), where agent, vector, and susceptible host coincide. There are numerous susceptible seasonal laborers and job-seekers coming to Addis Ababa and its environs. Historically, the war between the Mahdists and Christians on the Ethiopian Plateau in the 1880s is of interest. Few of the defeated Mahdists moved away but there was an exodus for religious reasons to Chad in 1894. Chad is on the pilgrimage path from West Africa to Mecca, as well as on the trade route from North Africa. When the followers of Rabih Zubair were defeated in 1900, they moved probably along the latter trail to Fezzan, Algeria, and Tunisia.[127] According to these authors relapsing fever was first diagnosed in the Adua and Axum outbreaks in 1918. Italian physicians in Ethiopia and British troops faced the disease during the war.[646] Ethiopian outbreaks have been recorded by several writers,[156,607,608,661,664,736] as well as the export of the disease to Kenya[296] and its movement from and to the Sudan.[411] Sparrow[664] and Bryceson et al[127] consider Ethiopia a highly important epidemic focus, with about 1000 cases and 5% mortality per year in Addis Ababa. Relapsing fever in Ethiopia is at home also in the South-West Highlands especially among seasonal coffee bean pickers, along the railroad from the Red Sea Coast, and in the lowlands of Jijiga, where the tick-borne form is also present.

Whereas *B hispanica,* an East Asian tick, followed the route of the Moslem Conquest to the West, *B recurrentis,* probably of African origin, spread by war and migration to all parts of the world except Australia, New Zealand, and Polynesia. Tick-borne borreliae have become louse-adapted in the laboratory but have not mutated into the epidemic strain. Lice do not transmit borreliae to their progeny by the transovarian (hereditary) route, which is contrary to most *Borrelia*-bearing ticks. Each vector-louse has to be infested individually, and less than 20% of the lice fed on patients are able to transmit the disease. The presence of infected man or some other, hitherto unknown reservoir appears to be a *condicio sine qua non* for the maintenance of relapsing fever caused by the epidemic strain, *B recurrentis,* or else tickborne borreliae mutate into a louse-borne type by a hitherto undiscovered mechanism. The continuity of louse-borne relapsing fever, demonstrated by Bryceson et al,[127] certainly speaks in favor of contiguous and continuous man-to-man transmission, while *O moubata* and lice feeding on the same persons in Africa yet offer food for thought and consideration along another course.

Endemic Relapsing Fever

Endemic relapsing fever is tick-borne. Its ecology coincides with that of *Ornithodoros* species carrying human pathogenic borreliae. The occurrence of this type of relapsing fever also depends on the frequency of contact between man and arthropod. Man and *Ornithodoros* meet according to the life habits of the species involved. *O moubata,* dwelling in huts inhabited by man, will have a greater and more frequent opportunity to feed on him and transfer borreliae to man than will *O parkeri,* which avoids human abodes. Man may, however, invade the habitats of the tick as a temporary visitor (hunter, vacationer, soldier, and so forth), or as a permanent resident when new lands are opened for cultivation and new roads are built.

Tick-borne relapsing fever is usually at home within the 24°C summer isotherm.[471] *Ornithodoros* do not live in the monsoon and rain forests. They occur in semidesert areas, but man seldom goes there. In colder climates these arthropods are active only during the warm season, but all year around in the tropics. The feeding time of the nymphs and adult ticks usually coincides with the period when relapsing fever is most frequent. In the Kashmir, however, ticks breed during the winter, but relapsing fever is most frequent in the summer[394] when man more often invades the habitats of ticks.

Lice have to be crushed to transfer *Borrelia.* They die as a result of such an injury and thus can infect only one person. However, ticks do not have to be damaged to transfer the borreliae they carry. A single *Ornithodoros* may infect a different person or animal at each feeding. Adult ticks usually transfer borreliae through their coxal fluid, which is excreted during or after feeding. Some ticks, especially young specimens and developmental forms, may transmit borreliae with their bite. Since ticks do not move far from their burrows, they infect only man and animals that enter their limited area. Some *Ornithodoros,* as *O moubata,* seldom move farther than about 20 meters under their own power. However, they can be carried by man or animals to new locations and may originate new endemic foci but not epidemics.

At present, the best known foci of tick-borne relapsing fever are in Northwest and West Iran,[591] in the desert-steppe regions of Central Asia,[564] in Azerbeidjan principally on the Aspheron Peninsula,[39,585] in Soviet Georgia,[746] Southwest Turkestan.[586] Turkmenia,[566] Kazakhstan,[651] Uzbekistan,[657] along the Southwest Littoral of the Mediterranean,[686] in the Arab countries,[36] Israel,[253] Kenya, Tanzania, and Uganda,[303] South Africa,[556] the Kashmir,[600] in the Western part of the United States,[69,740] especially in Oklahoma,[274] Kansas,[183] Texas,[195,722] Oregon,[218,283,356] and California.[70,652*] Only scattered cases have been reported in the United States with the exception of an incident involving a small scout troop which visited a cave infested with *O turicata* in Kansas (US Communicable Diseases Center report). Several other occurrences of tick-borne relapsing fever were discussed in the chapter on *Ornithodoros* and the borreliae carried by them.

Reports from South America are meager. Marinkelle and Grose[474] isolated an unidentified *Borrelia* species from a bat *(Natalus tumidirostris)* in the large Maceregue cave near San Gil, in Colombia. This indicates that borreliosis is still present in that country. Vigors Earle[705] reported tick-borne relapsing fever in Ecuador, Colombia, and Venezuela.

An interesting summary of the relationship of the types of human habitations to the tick population was published by Walton.[715] In regions where ticks are not infested in large numbers, the infection may be smoldering. An example is Madagascar, where *B duttonii* is maintained by transovarian passage in relatively few individual *O moubata.*[189,517] In Panama, the proportion of *Borrelia*-infested ticks may not have changed recently, but since canvas cots are replacing the old board or bamboo beds the ticks have been deprived of their hiding places, which has resulted in a lower infection rate in man.[182]

As stated, soldiers, hunters, laborers, and tourists entering tick-infested areas are frequent victims of relapsing fever.[137,182] Local inhabitants of endemic areas may have

**Thompson et al (JAMA 210:1045, 1969) recently called attention to tick-borne relapsing fever also in the State of Washington.*

acquired a certain degree of immunity during childhood.[73] Therefore, it is principally the newcomer who becomes ill in such regions.[705] This was the case in Cyprus during World War II where tick-borne *Borrelia* infestations were discovered also in local miners.[291,738] Tick-borne relapsing fever appeared in 41 soldiers entering native huts in Transvaal,[492] in troops and travelers moving along tick-infested roads in Madagascar,[189,430] in the caravanserais of Iran,[245,739] and in the mountains of California where hunters and vacationers had used abandoned huts often infested with ticks.[729] An episode of tick-borne relapsing fever in children who followed a porcupine into a cave was described in Palestine.[6] Bates et al[68] studied 6 cases in boys who went hunting in the Arriján area of Panama, were badly bitten by ticks, and developed relapsing fever. Konitzer[419] reported the occurrence of the disease in Arabs sleeping in a cave. Severe relapsing fever developed in soldiers visiting caves near Damascus.[625] Cooper[201] found infected soldiers who had acquired the disease in caves, old dugouts, tank traps, and trenches infested with rodents in Tobruk. An identical situation developed in Cyprus.[291,738] Ashbel[29] compared the strains isolated from soldiers in Tobruk and Palestine, and found some differences. But soldiers off duty also may acquire tick-borne relapsing fever, such as one who chased a porcupine into a cave near Jerusalem.[253]

Many infested ticks live in the desert areas of Africa,[471] in the less inhabited regions of Central Asia,[33,398,571] and in the Caspian area.[39,475,746] Their contacts with man are few, and therefore the human infection rate is low. Sometimes the tick vector is associated with domestic animals, as with sheep in the Kashmir,[394] and create a hazard to their tenders; or with fowl kept in living huts, as in East Africa.[432] The huts in East Africa abound with tick vectors of *Borrelia*.[338,340]

It is said that indigenous people from East Africa carry *O moubata* with them for good luck. This tick becomes easily domesticated. The relapsing fever in the Witwatersrand gold mines,[742] and among other migrant Africans in South Africa,[19] is a disease imported by man. Geigy[303] attempted to acquire "good luck" ticks from these people for investigating the borreliae in them but did not succeed. *O moubata* not dwelling with man is irregularly distributed in Africa but its ecology in the wild is the same as that of the warthog.[303,711] Geigy found it in the hair of warthogs which are hunted, and agrees with Walton[711] that the original habitat of *O moubata,* the vector of *B duttonii,* was probably with those animals but then the arthropod was transferred to huts by man carrying warthog pelts or carcasses.

Other *Ornithodoros* (principally *O tholozani)* move with caravans, on sheep, camels, and other animals driven from one place to another. and may make their homes in used or abandoned stop over places along the caravan route. Considering that *O tholozani* may live for more than 20 years and transmit the infection after 10 years,[108,568] the survival of *B persica*, the organism carried by it, appears to be rather well insured. One frequently encounters quite dried-out and apparently lifeless *O moubata* and *O tholozani* which avidly feed and return to normal at the first occasion when blood becomes available.

The parasite-vector-host relationships in relapsing fever may be delicately balanced, or the association may be based on less specific factors. There is no firm indication to date that the human louse feeds on mammals other than man outside the laboratory. Numerous *Borrelia*-bearing *Ornithodoros* bite several species of animals, whereas others display more selective food habits. *Ornithodoros* may use the burrows, caves, and other types of shelters of animals with or without feeding on them. The species of rodent or coldblooded animal inhabitants of such hiding places may change, but the tick may remain in the shelter because it often selects a particular habitat rather for the microclimate (temperature, moisture, etc.) than because of the animals living in it. If a tick infested with borreliae feeds on an animal, it does not necessarily infect the animal, and the mammalian host of the tick does not always become a reservoir of *Borrelia.*

Another factor that limits the role of mammals in the cycle of borreliosis is their reaction to the bite of the tick. Some ticks produce local analgesia. The bite of others is so painful that the animal will become aware of the tick and try to get rid of it. Several species of ticks feed for a long time, others for only 20 to 60 minutes. *Ornithodoros* that successfully transmit borreliae to man belong to the latter category. Those that are night-feeders and attack man in his sleep are the most effective propagators of borreliae. Baltazard et al[56] correlated the response of younger and older animals to tick bite and found that young animals, which are less able to rid themselves of ticks and which have a higher mortality rate when infected with *Borrelia,* become the prime victims of borreliosis when ticks are hatching and seek food. A more stable state develops when only mature animals are present in the burrows and dugouts.

The vector-host relationship becomes further involved when *Ornithodoros* seeks to share the shelters of domestic animals or feed on them. A broad field for cooperative studies in a hitherto little investigated area can be entered here.

PATHOLOGY

In terms of the present functional or "dynamic" concept of pathology, borreliosis is a disease characterized by cyclic responses to a cyclic agent. The problem is why these changes take place in man. Epidemics are not

always feasible for detailed studies because of the large number of patients to be treated, the habitually crowded and undermanned facilities in louse-infested areas as well as in sparsely inhabited regions where *Ornithodoros* thrives, and the lack of interest in this illness in advanced countries where the disease is rare, often merely meriting a case report in a local medical journal. Well-equipped laboratories, therefore, have resorted principally to animal experimentation in the past. The animal models used have been mostly rodents, which are phylogenetically remote from man, and do not permit drawing conclusions valid for human beings in all aspects. Nevertheless much of our present day knowledge of borreliosis is derived from rodent experiments, which will be summarized first.

Predisposition to borreliosis has not been studied to a great extent. One of the most important results of such investigations is that of Guggenheim et al[328,329] who demonstrated that protein and thiamine-deficient diet predisposes rats to severe *B persica* infection. This may have been due also to the concomitant caloric deficiency.

In young rats infected with *B merionesi,* the borreliae were found only inside veins, terminal arteries, capillaries, and sinusoids including those of the bone marrow but no inflammatory changes were noted and no phagocytosis. Small necrotic areas in different organs were due to obstruction of the circulation by blood coagula.[446] In other infections, in Central Asia, borreliae were always fewer in the blood than in the spleen of the rodents. Neither phagocytosis, nor disintegrating borreliae could be detected by Aravantinos.[22] Kritschewski and Singinshima[422] considered phagocytosis an accidental phenomenon in which fixed phagocytes do not play a role, and only dead organisms are attacked by phagocytes.

The reticuloendothelial system (RES) has been considered important in borreliosis because when it is blocked in otherwise resistant animals, these may become susceptible to borreliae.[126,736] Borreliae are destroyed in the body by antibodies, not by phagocytes.[393] The anatomy of the brain with respect to the blood supply apparently is the reason that borreliae are less exposed to antibodies in the central nervous system (CNS) than they are in the blood stream. It is not known, however, why the neurotropism of some borreliae differs from that of others.

Splenectomized animals often but not always had more borreliae in their circulation than surgically unaltered rodents. Pirot and Bourgain[581] but not Baltazard[46,50] found splenectomy more effective in producing serious *Borrelia* disease. In *B duttonii* infections there seemed to be some relationship between the reticulocyte response, the blood loss, the development of anemia, and the number of borreliae injected, in the trials conducted by Robertson.[605] *B persica* caused severe bleeding, including hemoperitoneum.[119] Kemp et al[404] observed splenic enlargement and a decrease of younger cells in the perifocal zones, only small lymphocytes in the germinal centers, some of these with pyknotic nuclei, and dilated sinuses tightly packed with red blood cells, without hemolysis and phagocytosis of the red blood cells in the splenic sinuses.

The so-called *B novyi* served in the experiments of Martinez Báez and Villasana.[470] They found the capillaries of the pia mater, cerebrum, and cerebellum, as well as the choroid plexus, congested. There was a microglial response in the cerebral cortex, and the cornu ammonis. No changes were apparent in the neurons. Lymphocytic infiltration of the pia with later absorption of small hemorrhages was observed. Garnham et al,[296] however, saw degeneration of the ganglion cells without meningovascular inflammation, in Kenya.

Rats infected with *B recurrentis* produced large amounts of lactic acid, followed by a blood carbon dioxide shift, hypoglycemia, and glycogen depletion.[385]

It is interesting to note that Horrenberger[372] found *B hispanica* also in the saliva of infected guinea pigs.

Kemp et al[404] believed that the periodicity of the disease in man is due rather to a refractory period of the borreliae than to antibody activity. In our concept, this statement has to be amplified and modified in view of recent clinical and experimental evidence. For instance, the development of antibodies against subsequent phase variants which begins shortly before the crisis[136] and steadily increases during subsequent attacks,[265,268,303] together with the slow ascent of the levels of avid antibody leading to firm antibody-antigen complexes in primates, may explain the dilatory evolution of immunity. The reluctance of borreliae to enter tissues and remain within the arteriovenous and capillary bed and interstitial spaces as well as the lack of participation of a considerable proportion of the RES may account for the slow process of antibody formation via the RNA-polysomal route.* The assumptions of Russell,[618] Belezki and Umanskaya,[72] and Bryceson et al[127] that antibodies immobilize and begin to lyse borreliae, after which phagocytosis may take place, with RES playing the role of a filter, was borne out by Anderson and Zimmerman[17] and others. Schofield et al[629] pointed out the role of leukocytes during the crisis which ends the attacks. The theory of such a role is based on immunoadherence[3] and leukotaxis which may unmask new determinants according to Bryceson et al,[127] particularly the release of endogenous pyrogen from these elements. Parry et al[562] demonstrated also that the white blood cells, which abruptly decrease in number before the crisis and return to normal after the borreliae disappear

**Our recent experiments in patas monkeys (Exp Mol Pathol 1970;12:255) demonstrated the role of tRNA-ribosomal participation in this process.*

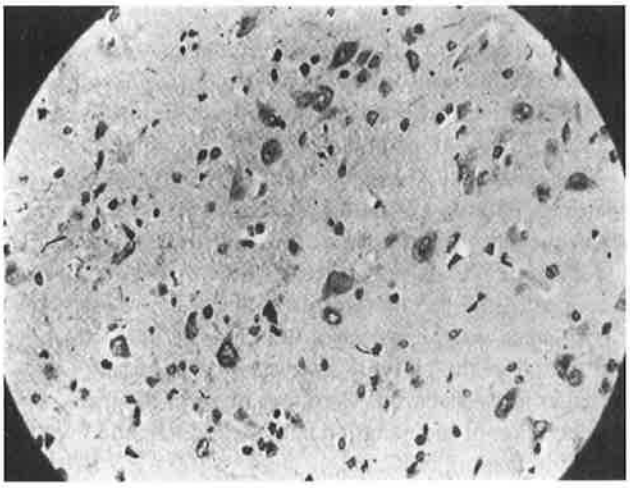


Figure 29. Gliosis and neuron cell damage in relapsing fever.

from the circulation, often are vacuolated and show loss of granules. Schofield et al[629] felt that this is rather sequestration than loss of a large number of cells because the serum muramidase (lysozyme) does not increase.

Russell[617,618] had already observed as early as 1930 that macrophages do not phagocytize borreliae but that pinocytosis (engulfing of dead fragments) takes place in them. Hindle[364] felt, however, that RES plays a greater role in the destruction of borreliae and that these cells actively respond to borreliae. Borreliae seem to break up in the spleen[618] but fixed phages do not engulf them there.[404] Anderson and Zimmerman[17] believed that the process in the spleen is of considerable importance for disposing of borreliae. It is not known how borreliae are actually killed,[631] principally since polymorphonuclear cells have been said to phagocytize only dead borreliae.[669] We join those who believe that the organisms appear to be destroyed by antibodies rather than by phagocytosis.[393,422,688]

Borreliae retreat to the central nervous system, the spleen, the liver, and the bone marrow after the primary attack and after each relapse.[68,133,235,591,620,640,731,732] As a result of infection with *Borrelia,* there are antibodies present against that organism, but the levels of antibodies in the cerebrospinal fluid are significantly lower than in the blood.[719] It is known, however, that borreliae penetrate the blood-cerebrospinal barrier.[281]

The literature on white blood cells is richly documented. Karwacki and Krakowska,[397] and Bryceson et al[127] found an increased white blood cell count in relapsing fever, with an abrupt fall just before the borreliae disappear from the blood, then a return to normal. Others[482,503] emphasized a shift to the left, with monocytosis and eosinopenia. In *B duttonii* infections, low eosinophil counts seem to be the rule.[437] The same observation was made in louse-borne relapsing fever.[387,127] Sulday,[672] in Madagascar, saw an increase in polymorphonuclear neutrophiles during the attack. Lymphocytes also increased while eosinophils decreased in number. Monocyte counts reached their lowest point just before the febrile episode, and their maximum at the beginning of the interim. Karwacki and Krakowska[397] found an increase in lymphocyte counts in the crisis; when this did not occur, a relapse followed. Other authors[175,176,590] made similar observations. Browse[114] did not find marked changes in the blood picture in his patients in Qetta.

Another feature of relapsing fever is the involvement of the blood circulation. Capillaries impacted with red blood cells, or a hemolytic tendency[17] due to lack of one or two coagulation factors,[127] may cause petechiae or more serious profuse bleeding, and ischemic, then necrotic foci in any organ. This may result in central nervous system, lung, gastrointestinal, and other disturbances. Considering further hematologic changes, the hemoglobin is usually low[404,503]; Más de Ayala[476] found it seldom unchanged. Bryceson et al[127] pointed out that in high altitudes such as in Addis Ababa the ratio of hemoglobin to the red cell count may differ from that at lower altitudes. Polychromasia and poikilocytosis[672]; progressive anemia of the hypochromic and normocytic type[388] in China; at times also hemolytic anemia[299] has been observed in Israel. Robinson[607] saw prothrombin deficit. This was measured by Bryceson et al[127] in terms of a prolonged prothrombin time. These authors also recorded lowered fibrinogen levels and decreased clotting ability of the blood. The bleeding time was unchanged. Few alterations in the serum chemistry were noted by Maruashvilli[475] in the Caucasus in mild tick-borne infections.

Cimmino[181] reported an increased blood sedimentation rate (BSR) both during attacks and remissions in Erithrea. Increased BSR was also registered in Somaliland[156] and in Israel.[253] The platelet count was nearly always low in Abyssinia and in Israel. Extensive hemorrhages may occur also in borreliosis in South America.[573] These and the petechial rash will be discussed under Clinical Symptoms.

The postmortem changes are not specific.[71] Russell[617] described focal necrosis in the spleen. El Ramly[255] saw infarcts, mostly in males, during the first attack of louse-borne relapsing fever, which often become septic. Perisplenitis, in addition to miliary necrosis, has been reported,[607] as well as miliary lesions, congestion, and infiltration around the follicles, sometimes with tangled masses of borreliae in the germinal centers, at times marginal leukocytic infiltrations accompanied by mononuclears and fibrin.[404]

A further feature of relapsing fever is hepatitis which was emphasized by Bryceson et al.[127] Mayer[482] believed

that borreliae stay in the liver and are slowly released during the attacks. The liver is sometimes enlarged and the lobules less distinct than normally. Kemp et al[404] reported parenchymatous degeneration with enlarged cells harboring pyknotic nuclei. The sinuses appeared narrow but congested, the endothelial cells prominent. The number of Kupffer cells may be increased. Judge and Perine[391] related similar findings. The disturbances in the liver functions are reflected in increased serum bilirubin, alkaline phosphatase, and the transaminases SGOT and SGPT values. These features were systematically studied by Bryceson et al[127]; and reported also by Ombati and Oijambo[553]; and Eisenberg et al.[253] The urine may be dark,[127] frequently with bile pigments.[476] Urobilin and urobilinogen were found in Cyprus[242] and in other localities where liver involvement was recorded. Liver damage apparently is a frequent finding in severe cases.

There may be renal changes, principally in the tubules. The kidney may be congested and enlarged. The cells of the convoluted tubules are often swollen, and irregular. Hyaline casts may be seen in the urine. The interstitial tissue shows cellular infiltration, but the Bowman capsules are seldom involved. Bryceson et al[127] often found proteinuria with leukocytes and also erythrocytes in the urine. Microscopic hematuria is said to be more common in tick than in louse-borne relapsing fever. Exceptions to this man-made rule were registered by Chang,[154] but renal infarcts are 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 CNS 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 CSF for 65 to 69 days.[582,583] Borreliae were found in the CSF, in the brain, as well as in brain tumors, in East Africa.[590] Increased globulin was observed in the CSF.[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 CNS, 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 described 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 USSR,[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°C to 40°C (102°F 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 minutes. However, it may show a broader range and wider variations.[476] Except in the socalled "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 USSR[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 louseborne 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 louseborne 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 USSR. 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. Saddleback 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. Meningeal 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] Preexisting 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] Postinfectious 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 2 1/2 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 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 USSR, 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 USSR, 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]

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 USSR,[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

Table 3. Summary of the course of relapsing fever.

		Tick-borne					
	Louse-borne	**USA**	**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 relapses[x]	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 CNS 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

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 five. 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 7fi to 11 days in the Abadan outbreak, each relapse lasting 2fi 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]

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 palpation. 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

Table 4. Summary of clinical pathologic findings during febrile periods.

Hemoglobin	very often depressed, 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 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 USA
Urine bile pigments	very frequently increased
Red blood cells in urine	frequently increased, very frequently increased in Africa

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 8000 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 6000 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 FUO (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 5000 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 xray, ECG, 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 million red blood cells, 210,000 platelets, and

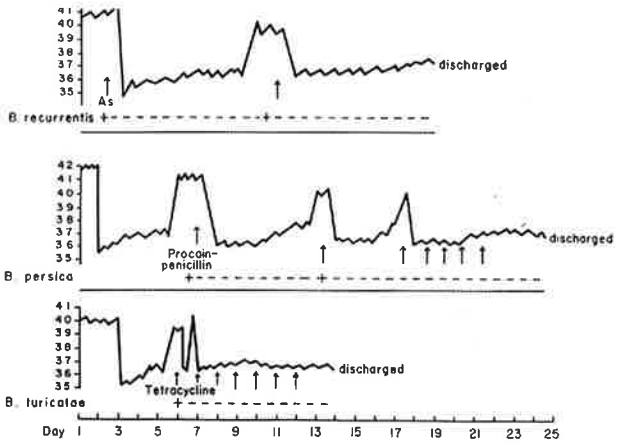


Figure 30. Fever curves of patients infected with various* Borrelia *strains.

7000 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 Figure 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 1fi 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 reevaluated 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, eg, 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 CSF. 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 CSF 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 6000 rpm, 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 $\times 100$ 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 1:1000 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[165] 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, eg, 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 test 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 percent 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, ie, 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 relapsing fever epidemics break out simultaneously.

The aggultinin titer with *Proteus OXK* was reported to be frequently 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, preinfection sera are not available from patients showing such reactions. The collection of post-convalescent scent 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 louseborne 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 (OF) 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 1000 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 borre-

liae.[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 2fi hours. The administration of 0.15 Gm in 6-hour intervals has also been helpful. Bryceson et al administered 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 1/ 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 timehonored 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 (Garnmexane®, 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 aroun d the base and doorwalls of the huts, kept ticks away for 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.

**Some governments are discouraging the general use of DDT.*

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 1000 sq ft. The floors of the huts and camps were dusted, as were a few inches of the bottoms of the walls. Retreatment 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 4/ cents per lb.

Fendall and Grounds[269] and Tesdale[678] were satisfied with the long-range effect of residual BHC application against *Orinthodoros.*

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 2000 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 alerted 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.

CHAPTER II

BORRELIOSIS IN DOMESTIC ANIMALS

Borrelia theileri

Borrelia theileri Lavern 1903 was isolated by Theiler in South Africa in 1902 from cattle with a mild disease

called tick spirochetosis.[681] The illness resembled piroplasmosis (cattle tick-fever). There were one or two attacks of fever, loss of appetite and weight, weakness, and anemia, but hematuria was rare. A similar disease was seen in sheep and horses. The causative agent, however, appeared to be the same in all three species of domestic animals.

B theileri is a slender *Borrelia,* 20 to 30 μ long, 0.2 to 0.3 μ wide, with 5 to 10 spirals, showing flexuous motion under the microscope. Smaller forms were seen in horses.

This *Borrelia* is transmitted by the African cattle tick *Rhipicephalus (decoloratus) evertsi.*

A similar disease in cattle was described recently in Australia by Callow.[138] The *Borrelia* was 6 to 19 μ long, with 3 to 7 large, wavy spirals, resembling the smaller form of *B theileri* from African horses. The infection was transmitted by nymphs of *Boophilus micropus*, an Australian cattle tick.

The mildness of the disease does not require treatment but tetracycline, 2 mg per Kg weight intravenously, will rid the animal of the borreliae.

Dipping cattle periodically is a measure helpful in eradicating ticks.

Other Borreliae

Borrelia hyos was described by King and Baeslack in 1913.[128] It was isolated from swine suffering from hog cholera. The organism is about 5 to 7 μ long and 1 μ wide. It can be grown in animal protein and tissue fragments containing media, but it is not the causative agent of hog cholera. Its taxonomy is doubtful.

Hjelle[367] described *Borrelia*-like organisms in the urine of lambs suffering from fever, icterus, photophobia, swollen eyelids, and facial eczema. No further data are available.

Dobell,[243] Hindle,[363] and others listed borreliae isolated from elephants and camels which were not studied further.

Borrelia suilla was reported by Kinmarsh in 1937 from ulcerative granulomas of pigs kept under unhygienic conditions in Australia and New Zealand. This organism should not, however, be classified with the borreliae.

CHAPTER III

AVIAN BORRELIOSIS

Knowles et al,[415] Lesbouyries,[445] and Loomis[459] presented excellent reviews of this subject.

Borrelia anserina and Its Transmission

The causative agent, *Borrelia anserina* Sakharoff 1891, was first seen in geese by Sakharoff in Siberia. Marchoux and Salimbeni[472] established the vector and isolated the organism from fowl in Brasil. The common fowl or "blue" tick, *Argas persicus* Oken 1818, is a vector. In Brasil, *A miniatus* was incriminated as the transmitting agent. The pigeon tick, *Argas reflexus,* is occasionally found infected with *B anserina* in the Old World.

Argas persicus was the vector in the outbreak of "range paralysis" of fowl in Texas between 1937 and 1939, which claimed a mortality of 27% to 91%.[113] Larvae and nymphs of *A persicus* were found infectious to White Leghorns in Texas[131] and in the USSR.[540] Transovarian transmission of *B anserina* in *A persicus* was emphasized.[361,415,541] The examination of the ova of *A persicus* for small forms of borreliae is a tedious task because granules of nonmicrobial origin are present in the ova.

Nikitina[541] stated that the saliva of *A persicus* also contains borreliae.

The red fowl mite, *Dermanyssus gallinae,* was suggested as an alternate vector. This mite remains infectious for only 3 days, and the organisms do not multiply in it according to Knowles et al.[415] Hungerford and Hart[376] also conducted experiments with *D gallinae* and were satisfied that it can transmit *B anserina.*

Zuelzer[747] could not find *Argas* in an outbreak along the Baltic Sea and proposed that *Culex* mosquitoes are vectors of *B anserina.* This was not confirmed by the experiments of Nieschulz and Bos,[539] who observed that while mosquitoes may take up *B anserina* the organisms disappear from the mosquitoes in a few days. Kapur[396] had the same results with *Anopheles albopictus.* McNeil et al[488] and Loomis,[459] studying epidemiology of infected turkeys in California, came to the conclusion that *B anserina* was transmitted by the feces of the infected birds, or by cannibalism as reported also from India.[666]

Artificially induced transmission of *B gallinarum* by *Ornithodoros moubata* was accomplished in the laboratory.[115,284]

The blood of the chickens is highly infectious for susceptible birds.

Borrelia anserina is 6 to 30, usually 8 to 20 μ long, and 0.2 to 0.3 μ wide, with 5 to 8 spirals of various length. It is actively motile with lashing movements. It was studied under the phase and the electron microscope[229,673] and its fibrils were observed.

The biochemistry of this *Borrelia* was investigated.[385,626,653,654] *B anserina* gives the impression of being a true anaerobic organism, but does not differ from other borreliae in its enzymatic systems.

B anserina can be stained or observed by darkfield illumination as can other borreliae. Gross and Ball[325] successfully used fluorescein-labeled antibody to demonstrate *B anserina.*

B anserina appears to survive in citrated blood at 0°C for 3 weeks but disintegrates in 10% saponin or bile solutions.

The organism can be cultured in Tyrode's solution or in coagulated egg white with 10% rabbit serum,[288] as well as on the chorioallantoic membrane or in the allantoic cavity of developing chick embryos.[91,487]

Kligler et al[413] demonstrated several serologically different types of *B anserina.* Saurinov and Delamater[623] used agglutination and precipitation tests for the serologic differentiation of *B anserina.* Convalescent serum kills the organisms. The borreliocidin (borreliolysin) in the convalescent serum is complement-dependent. Together with the immobilizine test the test for borreliocidin is very helpful in the diagnosis of the disease.[698*]

PATHOLOGY

The organism appears to remain in the organs although only Himmelweit[359] was able to demonstrate phagocytosis of live *B anserina. B anserina* has been found in the lung, liver, spleen, kidney, and brain of infected birds but was confined to vascular and interstitial spaces. Antigen has been demonstrated in the tissues.[325] Mathey and Siddle[477] studied the pathology in spontaneously infected Mongolian pheasants. There were ecchymoses under the skin, hyalin degeneration of the muscles, sometimes more extensive hemorrhages in subserosal spaces of the gizzard and the heart, eventually with necrotic foci. The spleen was small, whereas it is usually enlarged and mottled with hemorrhagic foci in turkeys afflicted with the disease. The liver is also enlarged with hemorrhages and focal necrosis. Reddy et al[601] in India found mild meningoencephalitis with perivascular infiltrates and gliosis, and necrotic foci in the kidneys as in infected chickens. The lymph nodes are often enlarged. There is catarrhal enteritis.

COURSE OF THE DISEASE

The disease caused by *B anserina* is often called avian spirochetosis. Clinically, it begins after an incubation period of approximately 3 to 8 days, usually 4 days. The birds are cyanotic and have yellowish-greenish diarrhea, appear restless, then crouch with closed eyes. If they move, ataxia may become evident. Paralysis of the wings may be present. The body temperature reaches 43°C (109.5°F) or more in 2 to 3 days, sometimes later, and returns to 40°C (104°F) in about a week in those birds which survive the attack. The disease may last about two weeks.

Gabritschewsky in 1898 carried out a long series of experiments to demonstrate the immunologic features of avian borreliosis. Hoffman and Jackson[368] proved the identity of the disease in chickens, ducks, and turkeys. Doves, pigeons, grouse, canaries, and in the laboratory also turtledoves and sparrows acquired the infection. In some epidemics, more female than male birds become ill. Death oftern occurs on the 3rd or 4th day of the disease. The mortality rate may be higher in adult than in younger birds.

Young rabbits can be infected with intravenous injections of *B anserina* but the organisms disappear in a few days. Guinea pigs, mice, rats, monkeys, and cold-blooded animals are not susceptible to *B anserina.*[86,415,459]

No relapses are observed. Immunity or premunition develop, lasting for several months[409] or a year.[254]

B anserina infections have been reported from Europe, Siberia, India, Africa, Australia, Indonesia, South and Central America, lately also from the Southwest and Western regions of the United States and Canada.[368,369,399,415,459,477,718] Apparently transmission by feces of infected birds is noted more often at present than in the past.

Treatment and Prevention

Packchanian[559] discussed chemotherapy. Penicillin is usually recommended as procaine penicillin, intramuscularly, 100,000 units. Adult chickens may be given 5000 to 10,000 units divided in 5 to 6 doses over a period of 12 to 15 hours. Baby chicks may require much higher doses.

Diaz Ferrón[238] recommended tetracycline, 125 mg per day. In Europe, oxytetracycline, 2 mg per Kg body weight, is given in one dose, intramuscularly.

Landauer[431] recommended freshly collected blood of infected birds heated to 56°C for 30 minutes as a vaccine. Kolev[418a] in Bulgaria immunized one-year old birds with 1 mL formolized egg-grown vaccine. Ninety-six percent of the immunized fowl remained resistant to the disease for one year but only birds older than 4 months responded favorably.

Dickie and Barrera[239] demonstrated that after an outbreak the flock does not harbor the disease for longer than 30 days. General hygienic procedures and quarantine, coupled with antibiotic treatment, should, therefore, be successful.

CHAPTER IV

BORRELIAE FROM MUCOUS MEMBRANES

Borreliae from mucous membranes are usually listed as *Borrelia buccalis* and *Borrelia vincentii* from the mouth and from the respiratory tract, and *Borrelia refringens* from the genitalia.

Data on these organisms are confused and meager, because the oral cavity under conditions considered normal, as well as ulcerative-necrotic lesions with low oxygen tension, may harbor organisms morphologically resembling borreliae.

**Recently Soumrov et al. (Zbl Vet Med 1969;16:328) reported excellent results with the precipitin test. Al-Hilly (Am J Vet Res, 1969;30:1877) recommended immunodiffusion as a particular serologic test.*

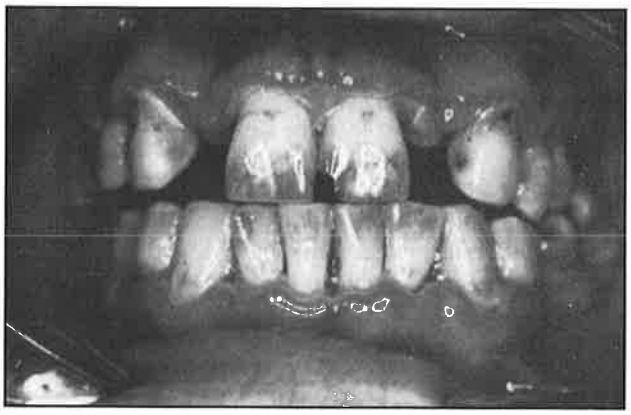


Figure 31. Necrotic ulcerative areas between and around the maxillary front teeth, and the central incisor region. Some necrotic and ulcerative areas also around the anterior mandibular teeth. Description and photograph courtesy of M.N. Wilderman, DDS, Professor and Head, Department of Periodontology, Louisana University School of Denistry, New Orleans, LA.

Borrelia vincentii was described by Vincent in 1896 as the cause of the so-called fusospirochetal infections, among which is Vincent's angina.[706] Uohara and Knapp[695] presented a review of oral lesions associated with this organism.

B vincentii is 5 to 10 μ long, and has 3 to 8 irregular spirals. Long, filamentous forms have been observed frequently in cultures. Bladden and Hampp[79] studied the ultrastructure of this organism. It has a triple-structured wall, with cylindrical protoplasm. and intracellular concentric laminations. There are an axial filament and several fibers, usually terminating in small knobs, as well as a large number of fibrils.

Not all strains produce metabolic gas.[423]

Canale-Parola et al[142] described a medium for the culture of *B vincentii.* This consists of desiccated Spirolate Broth (Baltimore Biological Laboratory) 1 Gm, desiccated Brain Heart Infusion Broth (BBL) 1.66 Gm, sodium thioglycollate 22.25 mg, asparagine 25 mg, Tryptone (Difco) 25 mg, gelatin 2 Gm, and distilled water 90 mL. The pH is adjusted to 7.0. After sterilization, 10 mL inactivated rabbit serum are added.

B vincentii is susceptible to lysis by lysozyme.[518] Antigenically, it differs from other treponemes.[493]

Fusiform bacilli are frequently found in lesions together with *B vincentii.* Tunnicliff[692] suggested that they are different phases of the same organism.

B vincentii has been isolated from acute gingivitis with painful edematous, and ulcerated interdental papillae and marginal gingivae, from ulceronecrotic gingivostomatitis, aphthous lesions, pharyngeal ulcers and tonsils covered with strongly adherent, dirty, gray membranes, peritonsillar abscess, regional lymphadenitis, and lung lesions. The disease has been designated as trench mouth, Vincent's disease. Vincent's angina, ulceronecrotic gingivostomatitis ulceromembranous stomatitis, pseudomembranous gingivitis, fusospirochetal disease, and so on. Pain, malaise, fetid breath, bleeding, salivation, and sometimes fever with leukocytosis, shift to the left, increased blood sedimentation rate, and at times gangrene are present. When the infection is restricted to the mouth, punched-out, easily bleeding ulcers of the gums are seen. Pseudomembrane formation, noma, gangrenous laryngitis, and destruction of the gums to such an extent that the teeth fall out, as well as erosions of the bones of the oronasopharyngeal region, have been ascribed to *B vincentii.* If the buccal mucosa is involved, more diffuse pseudomembranous lesions develop. Rectal and vaginal lesions have been reported.

The disease is more common in the undernourished, principally in children, and during wartime and other disasters.[13] It has been suggested that lack of one or more vitamins may predispose to this infection.

Black[78] emphasized, however, that herpetic infections may cause acute gingivostomatitis. He investigated the oral cavity of healthy children for the presence of *B vincentii* and found this organism in 60%, of those examined. Fusiform bacilli were demonstrated in 94% of the same group, and *B vincentii* and fusiform bacilli together in 18% to 63% of the children, according to age. It is, therefore, difficult to ascribe primary pathogenicity to *B vincentii.*

Malberger[466] in Gambia observed necrotic and ulcerative lesions of the interdental papillae in poorly nourished children with inadequate oral hygiene with numerous *B vincentii* present. Goldberg,[319] Uohara,[694] van der Veld,[703] and Knox[416] reviewed "trench mouth" and acute ulcerative gingivitis. Apparently, opinions concerning the pathogenic role of *B vincentii* are divided.

The differential diagnosis must consider diphtheria, coccal infections, and malignancy.

Hydrogen peroxide, antibiotic lozenges, and zinc paste locally, and recently Metromidazole®[275] have been recommended. A mouth wash with tepid 5% to 10% sodium bicarbonate or saline is often prescribed. Vitamins C and B complex are frequently administered. A patient with gingivitis belongs under the dentist's care.

Vincent's angina and related deeper lesions are treated either with procaine penicillin, 600,000 units daily, intramuscularly, or with tetracycline, 20 mg per Kg body weight orally, for one week.

It may be added that reports on long lasting *B refringens* infections still appear when vulvovaginitis and balanitis are discussed in East Europe[671] but other organisms, including *Mycoplasma*, are considered the causative agents in the West.

ACKNOWLEDGMENTS

This monograph could never have gone to press without the unselfish aid, help, and support of two persons. One of them, Dr. Addine G. Erskine, spent innumerable hours correcting, retyping, editing, proofreading, and indexing this volume. Busy as she was as Director of the Gradwohl School of Laboratory Technique and with numerous professional organizations, other editorial tasks, and ranching (unfortunately or fortunately, no B theileri has been isolated from her stock), she has always found time to cooperate on my writing ventures, including this monograph. I am sincerely and deeply indebted to her for all her most valuable help.

The other, Dr. W. Burgdorfer, Senior Medical Entomologist of the USPHS Rocky Mountain Laboratories, has never hesitated to replenish my stock of Ornithodoros *whenever my "tickorium" went out of gear. I am very much grateful to him for all support he has so kindly furnished during the years, in addition to admiring his elegant experiments and publications.*

Dr. W.E. Greer, Director of Animal Resources, Gulf South Research Institute, New Iberia, La., kindly checked the chapters on animal borreliosis. Most of the entomological statements which appeared 5 years ago were reviewed by Prof. G. Anastos, University of Maryland, and Prof. A. Rafyi at that time.

I am much obligated and sincerely grateful to Dr. A.D.M. Bryceson and his colleagues for permitting me to read and to quote their outstanding clinical study of relapsing fever in Ethiopia before publication, and to Dr. H. Hoogstraal for his encouragement.

Dr. T.C. Orihel, Adj. Professor of Parasitology, Tulane University, spent much valuable time and great effort providing me with and photographing arthropods for this book. His assistant, Mrs. B. van Duym, furnished several excellent drawings. Mrs. W. Martin of the Medical Illustration Service of this Center made additional valuable graphs. Dr. C. Jones, Smithsonian Institute, kindly selected and put at my disposal his photographs of Southeast African huts and rodent burrows. Dr. Jones also corrected and rectified the names of the mammals.

Dr. M.N. Wilderman, DDS, MS, Professor and Head, Department of Periodontology, Louisiana University School of Dentistry, kindly furnished the photographs of Vincent's disease.

Mrs. M. LaCroix and Mrs. C. Bennett typed and retyped the numerous drafts as well as the final copy of the manuscript. Their diligence and help are appreciated greatly.

APPENDIX

KRAJIAN'S "20 MINUTE" RAPID STAINING METHOD OF TREPONEMATACEAE IN FROZEN SECTIONS*

REAGENTS

1. Uranium nitrate .....1 gm
   95% Formic acid, C.P. .....3 ml
   Glycerin, C.P. .....5 ml
   Acetone, C.P. .....10 ml
   95 % Ethanol .....10 ml
2. 1% Silver nitrate solution, made up just before use from a 10% aqueous stock solution. The stock solution keeps for months in a dark bottle. The 1% working solution should be used the same day, not more than 3 times. Solutions with a brownish tinge are discarded.
3. Gum mastic solution.
   Saturate Absolute ethano .....35 ml
   with Gum mastic .....25 ml
   Let stand for 3 to 5 days in dark bottle at room temperature, shaking occasionally. Use the supernate.
4. Developer.
   Mix 40% Formaldehyde .....2.5 ml
   Acetone C.P. .....2.5 ml
   Dissolve in this mixture
   first Hydroquinon .....0.31 Gm
   then Sodium sulfite .....0.1 Gm
   and Pyridine .....2.5 ml
   Add to above solution #3 .....2.5 ml
   then Distilled water .....15 ml
   The developer should not be used more than 3 times. The solution will keep for 1 or 2 weeks in a dark bottle at room temperature. It should be replaced if a sediment is formed.
5. Thin celloidin solution. (Krajian formula).

PROCEDURE

a. Tissues fixed in 10% formalin at 67°C for 10 minutes are preferred. They are then frozen and sections, 7 to 10 μ thick, are washed in distilled water.

b. Prewarm solutions #1 and #4 in small Stender dishes in a paraffin oven at 60°C.

c. Prepare 3 Stender dishes with distilled water, one with about 5 to 10 mL 95% ethanol, another with 5 mL 95% ethanol to which a few drops of solution #3 have been added with a small glass lifter. (Note: metal instruments and tap water should not be used in this procedure).

d. Put the freshly made solution #2 in a 250 mL Pyrex or Kimex beaker.

e. Place the section in solution #1 at 56°C to 60°C in the paraffin oven for 5 minutes.

f. With a glass lifter, carry it to a Stender dish with distilled water. The section should open and float. Then pass 3 times quickly but gently through the Stender dish with 95% ethanol and mastic (see under c.).

Rinse in distilled water in a Stender dish. The section should spread out.

h. Transfer the section to the beaker with solution #2. Heat the contents of the beaker to 70°C to 73°C for 2 minutes, while exposing it to the light of a 60 W electric bulb from a distance of 4 ft.

i. Transfer the section on the glass lifter to the warm solution #4, lifting it in and out of the solution, exposing every part to the electric light and taking care that the section opens up every time it is put back into the solution. Repeat this 6 to 8 times. The tissue should appear brown.

j. Transfer to 95% ethanol to remove excess gum mastic.

k. Transfer to distilled water. If the tissue does not spread out, repeat step j for a few seconds and return section to distilled water.

l. Place the section again into the now cool solution #2 and expose to the electric light for another 10 to 30 seconds. This step is very important. Too cold or too warm silver nitrate solutions may cause improper results.

m. Transfer to a large dish with distilled water, then to a glass slide.

n. Dehydrate with isopropanol dropping it gently onto the surface of the section and leaving for about 30 seconds, blowing first gently, then harder to remove the water.

o. Blot gently with several thicknesses of Whatman No. 1 filter paper, then apply isopropanol anew to the slide for 1 minute. Drain and blot again.

p. Dip once in #5 solution. Wipe the bottom of the slide dry. Blow gently at the surface until the celloidin is dry.

v. Dehydrate in a staining dish with isopropanol for 1 minute.

r. Carry through two changes of xylene for several minutes each.

s. Clean excess celloidin around the tissue and mount in gum damar.

Treponemataceae, including borreliae, appear black against a yellow or brownish background.

Thi s method is applicable to paraffin sections but the period of staining has to be doubled.

**Krajian AA. Am J Syph 1939;23:617. Krajan AA,Gradwohl RBH. Histopathological Technic, 2nd ed. C.V. Mosby Co., St. Louis, Mo., 1942. Frankel S, Reitman S. (Editors). Gradwohl's Clinical Laboratory Methods and Diagnosis, 6th ed. C.V. Mosby Co., St. Louis, Mo., 1963. The above is a revision by Dr. Addine G. Erskine.*

REFERENCES

1. Ackerman V, Protasov N. Arch Schiff Trop Hyg 1936;40:352.
2. Addamiano L, Babudieri B. C R 1st Super Sanita 1957;20:440.
3. Adler S, Ashbel R. Ann Trop Med Parasitol 1937;31:89.
4. Adler S, Ashbel R. Ann Trop Med Parasitol 1942;36:83.
5. Adler S, Theodore O, Schieber H. Lancet 1936;i:448.
6. Adler S, Theodore O, Schieber H. Ann Trop Med Parasitol 1937;31:25.
7. Adler S, Yoeli M, Meerovitch E. Trans R Soc Trop Med Hyg 1952;46:159.
8. Aeschlimann A. Acta Trop 1958;15:15.
9. Aeschlimann, A. Acta Trop 1964;21:1.
10. Aeschlimann A, Geigy R, Hecher H. Acta Trop 1968;25:176.
11. Alexandrov YM. Soviet Med 1940;2:19.
12. Alline M, Marx R. Ann Inst Pasteur 1966;111(suppl):28.
13. Alnamo J. Sotilaslaak Aikak 1966;41:73.
14. Amiraian K, Leikhim EJ. Immunology 1966;10:349.
15. Anastos G. The Ticks of Ixodides of the USSR. A Review of Literature. US Public Hlth Svc Publ 1957;548.
16. Anderson TF. East Afr Med J 1947;24:259.
17. Anderson TR, Zimmerman LE. Am J Pathol 1955;13:1083.
18. Anduze PP. Bol Entomol Venezol 1943;2:149.
19. Annecke S, Quinn P. S Afr Med J 1952;26:455.
20. Anonymus. Rel Epidem Hebdomad Org Mond Santé 1969;44:425.
21. Arakhcheva SG. Med Parasit Parasit Bolez 1963;32:665.
22. Aravantinos A. Ann Inst Pasteur 1919;33:425.
23. Arboni E. Boll Ist Sieroterap Milan 1929;8:813.
24. Aristowsky WM, Hoeltezer RR. Zbl Bakt Abt I Orig 1929;112:44.
25. Aristowsky WM, Wainstein AB. Ztschr Immunfschg Exp Ther 1929;61:296.
26. Arthur DR. Ticks. Cambridge, England: Cambridge University Press; 1960.
27. Arthur DR. Ticks and disease. Evanston, IL: Row, Peterson & Co.; 1962.
28. Ashbel R. Ann Trop Med Parasitol 1942;36:97.
29. Ashbel R. Trans R Soc Trop Med Hyg 1949;42:409.
30. Atkey OHP. Bull Offic Int Hyg Publ 1929;21:1932.
31. Aubin IA, Gachkel Z, Gallo M. Algérie Méd 1947;1:408.
32. Auboni E. Boll Ist Milano Sieroterap 1929;8:813.
33. Avanessov GA. Med Parazit Patazit Bolez 1938;7:88.
34. Babudieri B. C R 1st Super Sanità 1948;11:1067.
35. Babudieri B. C R 1st Super Sanità 1952;15:711.
36.Babudieri B. Bull World Health Organ 1957;16:911.
37. Babudieri B. Zbl Bakt Parasit Abt I Orig 1968;91:386.
38. Babudieri B, Bociarelli D. J Hygiene 1948;46:438.
39. Bairamova RA. Azerbaidzan Med Zhurn 1958;11:72.
40. Bairamova RA. J Mikrobiol Epidemiol Immunol 1963;9:83.
41. Baker EW, Wharton GW. An Introduction to Acarology. New York, NY: The Macmillan Co.; 1952.
42. Balashov YS. Parazitologiya 1968;2:193.
43. Ballif L, Constantinesco N, Chelaresco M. Presse Méd 1947;55:586.
44. Balozer L. Bull Soc Pathol Exot 1948;41:146.
45. Baltazard D. Bull Soc Pathol Exot 1936;29:667.
46. Baltazard M. Arch Inst Hessarak 1946;4:57.
47. Baltazard M. Bull Soc Pathol Exot 1947a;40:77.
48. Baltazard M. C R Acad Sci 1947b;225:82.
49. Baltazard M. C R Acad Sci 1947c;225:1858.
50. Baltazard M. Ann Parasit Hum Compar 1954;29:13.
51. Baltazard M, Bahmanyar M, Habibi A, Mofidi C, Seydian B. Bull Soc Pathol Exot 1950;43:309.
52. Baltazard M, Bahmanyar M, Mofidi C. Ann Inst Pasteur 1947;73:1066.
53. Baltazard M, Bahmanyar M, Mofidi C. Bull Soc Pathol Exot 1948;41:141.
54. Baltazard M, Bahmanyar M, Mofidi C. Bull Soc Pathol Exot 1950;43:595.
55. Baltazard M, Bahmanyar M, Pournaki R, Mofidi C. Ann Parasit Hum Compar 1952;27:311.
56. Baltazard M, Chamsa M, Chirzadi M. Proc 8th Congress Trop Med Malar 1968;2:890.
57. Baltazard M, Chamsa M, Seydian B. Bull Soc Pathol Exot 1954;47:878.
58. Baltazard M, Habibi A. Bull Soc Pathol Exot 1954;47:48.
59. Baltazard M, Mofidi C, Bahmanyar M. C R Acad Sci 1947;224:1858.
60. Baltazard M, Mofidi C, Bahmanyar M. Bull Soc Pathol Exot 1948;41:399.
61. Baltazard M, Mofidi C, Bahmanyar M, Seydian B. C R Acad Sci 1947;225:82.
62. Baltazard M, Pournaki R, Chabaud AG. Bull Soc Pathol Exot 1954;47:589.
63. Baltazard M, Seydian B, Mofidi C, Bahmanyar M. Bull Acad Natl Med 1949;133:284.
64. Balteanu I. Arch Romain Pathol Exp Microbiol 1947;14:170.
65. Balteanu L, Russ M, Voiculescu M. Arch Romain Pathol Exp Microbiol 1948;15:310.
66. Bannister K. Southwest Med 1930;14:581.
67. Banwell JG, Kibukamusoke JW. East Afr Med J 1963;20:124.
68. Bates LB, Dunn LH, St. John JH. Am J Trop Med 1921;1:183.
69. Beck MD. J Infect Dis 1937;60:64.
70. Beck MD. Am Assoc Adv Sci Symposium No 18, 20;1942.
71. Beeson PB. In: Harrison TR and Editorial Board. Principles of Internal Medicine, 2nd ed. New York, NY: Blakiston Co.; 1954.
72. Belezki WK, Umanskaya RM. Virchows Arch Pathol Anat Physiol 1929;272:305.
73. Bell S. J Trop Med Hyg 1956;59:82.
74. Benedetto V di. Arch Ital Sci Med Colon Paras 1941;20:168.
75. Berks G, Goodwin LG. Nature 1951;167:447.
76. Bianchi C. Med Ital 1947;27:200.
77. Bijlmer J, Antonie van Leeuwenhoek. J Microbiol Serol 1952;18:246.
78. Black WC. Am J Dis Child 1938;56:126.
79. Bladen HA, Hampp EG. J Bacteriol 1964;87:1180.
80. Blanc G, Bruneau J. Bull Soc Pathol Exot 1951;44:313.
81. Blanc G, Bruneau J. C R Acad Sci 1956;242:1376.
82. Blanc G, Bruneau J, Chabaud A. C R Acad Sci 1951;234:2577.
83. Blanc G, Bruneau J, Pages R. Bull Acad Natl Méd Paris 1949;133:600.
84. Blanc G, Maurice A. Arch Inst Pasteur Maroc 1949;3:613.
85. Blanc G, Noury M, Fischer M. Bull Acad Nat Méd Paris 1933;109:587.
86. Bodechtel G. Ztschr Hyg Infektkrk 1930;111:348.
87. Bodman RI, Stewart IS. Brit Med J 1948;i:291.
88. Böger A. Münch Med Wochenschr 1943;90:549.
89. Bohls SW. Am Assoc Adv Aci Symposium No. 18 1942;125.
90. Bohls SW, Irons JV. Am Assoc Adv Sci Symposium No. 18 1942;42.
91. Bohls SW, Irons JV, De Shazo T. Proc Soc Exp Biol Med 1940;45:375.
92. Bohls SW, Schuhardt VT. Texas State J Med 1933;29:188.
93. Boiron H. Ann Inst Pasteur 1947;73:49.
94. Boiron H. Bull Méd Afr Occident Franc 1948;5:173.
95. Boiron H. Ann Inst Pasteur 1949a;77:620.
96. Boiron H. Bull Soc Pathol Exot 1949b;42:13.
97. Boiron H. Bull Soc Pathol Exot 1949c;42:62.
98. Boiron H. Bull Soc Pathol Exot 1949d;42:91.
99. Boiron H, Koerber R, Carronnier B. Bull Soc Pathol Exot 1948;41:81.
100. Bonné G. Ann Soc Belge Méd Trop 1939;19:477.
101. Bormon FV. Deutsch Med Wochenschr 1943;69:356.
102. Borrel A. C R Soc Biol 1906;60:138.
103. Borrel A, Marchoux E. C R Soc Biol 1905;58:362.
104. Bruen F, Blatter C. Helv Chim Acta 1960;43:1690.
105. Bourgain M. Bull Soc Pathol Exot 1946;39:185.
106. Bourgain M. Ann Inst Pasteur 1947;73:84.
107. Bourgain M. Bull Soc Pathol Exot 1950a;43:689.
108. Bourgain M. Bull Soc Pathol Exot 1950b;43:692.
109. Bradfield JRG, Carter DB. Nature 1952;109:944.

110. Brett GA. Bull Entomol Res 1939;30:247.
111. Briggs LH. JAMA 1922;79:941,
112. Brissolese A. Arch Ital Sci Med Colon Parass 1938;19:377.
113. Brown JC, Cross JC. Science 1941;93:528.
114. Browse GV. Indian Med Gaz 1912;47:387.
115. Brumpt E. Bull Soc Pathol Exot 1908a;1:577.
116. Brumpt E. Bull Soc Pathol Exot 1908a;1:579.
117. Brumpt E. C R Acad Sci 1926;183:1139.
118. Brumpt E. C R Soc Biol 1933;113:1169.
119. Brumpt E. Bull Soc Pathol Exot 1934;27:510.
120. Brumpt E. Ann Parasitol Hum Compar 1936a;14:436.
121. Brumpt E. Ann Parasitol Hum Compar 1936b;14:640.
122. Brumpt E. Ann Parasitol Hum Compar 1937;15:75.
123. Brumpt E. C R Acad Sci 1939;208:2029.
124. Brumpt E, Brumpt LC. Ann Parasitol Hum Compar 1939;17:287.
125. Brussin AM. Ztschr Immun Exp Ther 1925;44:328.
126. Brussin AM, Sternberg EJ. Giorn Batter Immun 1938;21:46.
127. Bryceson ADM, Parry EHO, Perine LL, Vukotich D, Warrel DA, Leithead CS. Quart J Med 1970;39:129.
128. Buchanan RE (Ed). Bergey's Manual of Determinative Bacteriology, 8th ed. Baltimore, MD: Williams & Williams; 1958.
129. Burgdorfer W. Acta Trop 1951;8:193.
130. Burgdorfer W, Varma MGR. Ann Rev Entomol 1967;12:347.
131. Burroughs AL. Science 1947;105:577.
132. Burrows W. Textbook of Microbiology, 19th ed. Philadelphia: W.B. Saunders Co.; 1968.
133. Buschke A, Kroó HV. Klin Wochenschr 1922;1:2470.
134. Buxton PA. Biol Rev 1932;7:275.
135. Buxton PA. The Louse. Baltimore, MD: Williams & Wilkins Co.;1946.
136. Calabri O. J Exp Med 1959;110:811.
137. Calero C. Am J Trop Med 1946;26:761.
138. Callow LL. Br Vet J 1967;123:492.
139. Calwell WK. Lancet 1920;i:785
140. Cambournac FJC, de Alemida Roque R, Ferreira Res J. Clin Contemp (Lisabon) 1951;5:524.
141. Caminopetros J, Triantaphyllopoulos E. Ann Parasitol Hum Compar 1936;14:429.
142. Canale–Parola E, Udris Z, Mandel M. Arch Mikrobiol 1968;63:385.
143. Cantacuzène J. Bull Soc Pathol Exot 1920;13:269.
144. Carley JG, Pope JH. Aust J Exp Biol Med Sci 1962;40:255.
145. Carlisle RJ. J Infect Dis 1906;3:233.
146. Carminati GM. Boll Ist Sieroterap Milano 1955;34:503.
147. Carminati GM. Boll Soc Ital Biol Sper 1956;32:923.
148. Carminati GM. Boll Ist Sieroterap Milano 1957;36:197.
149. Casaux J. Rev Méd Hyg Trop 1912;9:97.
150. Chabaud A. Bull Soc Pathol Exot 1939;32:483.
151. Chagin KP, Ditalov AG. Med Parazit Parazit Bolez 1960;29:288.
152. Chakrabarty A. J Indian Med Assoc 1949;18:352.
153. Chamsa M. Pathol Biol 1960;8:69.
154. Chang SL. Chinese Med J 1938;54:163.
155. Chapcheff C. Bull Soc Pathol Exot 1925;18:97.
156. Charters AD. Trans R Soc Trop Med Hyg 1942;35:271.
157. Charters AD. Trans R Trop Med Hyg 1950;43:427.
158. Chen KC. Proc Soc Exp Biol Med 1941;46:638.
159. Chen YP, Anderson HH. Proc Soc Exp Biol Med 1941;46:658.
160. Chen YP, Zia SH, Anderson HH. Am J Trop Med 1945;25:115.
161. Chernyshova TF. Med Parazit Prazit Bolez 1967;36:476.
162. Cherry JKT. Trans R Soc Trop Med Hyg 1955;49:563.
163. Chiao SM. Acta Brevia Sinensica 1945;1:4.
164. Chiriboga JM. Crónica méd Lima 1919;36:127.
165. Chohan IS. Armed Forces Med J India 1966;22:37.
166. Chohan IS. Indian J Pathol Bact 1967;10:289.
167. Chorine V, Colas–Belcour J. Bull Soc Pathol Exot 1947;40:383.
168. Chorine V, Crougue O. Ann Inst Pasteur 1942;68:518.
169. Chorine V, Crougue O. Bull Soc Pathol Exot 1943;36:262.
170. Chorine V, Grabar P, Tixier R, Crougue O. Ann Inst Pasteur 1943;69:162.
171. Chuaryan KhA. Zhurn Eksp Klin Med 1966;6:39.
172. Chung HL. China Med J 1936;50:1723.
173. Chung HL 10th Congress Far East Association of Tropical Medicine Hanoi 1938a;2:309.
174.Chung HL. Proc Soc Exp Biol Med 1938b;38:97,
175. Chung HL. Trans R Soc Trop Med Hyg 1938c;31:625.
176. Chung HL, Chang FC. Chinese Med J 1939;55:6.
177. Chung HL, Feng LC. Chinese Med J 1936;50:1 and 181.
178. Chung HL, Feng LC. Chinese Med J 1938;suppl 2:563.
179. Chung HI, Wei LY. Am J Trop Med 1938;18:661.
180. Cimino V. Boll Soc Ital Med Ig Trop Sez Eritrea 1942;1:45.
181. Cimino V. Bull Soc Ital Med Ig Trop Sez Eritrea 1943;2:76.
182. Clark HC. Am Assoc Adv Sci Symposium No. 18, 1942;29.
183. Closson HO. J Kansas Med Soc 1934;35:53.
184. Coffey EM, Eveland WC. J Infect Dis 1967a;117:23.
185. Coffey EM, Eveland WC. J Infect Dis 1967b;117:29.
186. Coghill NF, Gambles RM. Ann Trop Med Parasit 1948;42:113.
187. Coghill NF, Lawrence J, Ballantine ID. Br Med J 1947;i:637.
188. Colas–Belcour J. Pathol Biol Sem Hôp 1960;8:73.
189. Colas–Belcour J, Néel R, Vervent G. Bull Soc Pathol Exot 1952;45:69.
190. Colas–Belcour J, Vervent G. Bull Soc Pathol Exot 1949a;42:447.
191. Colas–Belcour J, Vervent J. Bull Soc Pathol Exot 1949b;42:470.
192. Colas–Belcour J, Vervent G. Bull Soc Pathol Exot 1955;48:747.
193. Coleman GE. Am J Public Health 1934a;24:1056.
194. Coleman GE. J Infect Dis 1934b;54:1.
195. Coleman JM, Wright HE. Am Assoc Adv Sci Symposium No. 18, 1942;26.
196. Coles AC. J Trop Med Hyg 1936;39:77.
197. Connor RC. Proc Med Assoc Isthmus Lis Canal Zone 1917;10:67.
198. Cook AR. J Trop Med Hyg 1904;7:24.
199. Cooley RA. Am Assoc Adv Aci Symposium No. 18. 1942;77.
200. Cooley RA, Kohls, GM. Argasidae of North America, Central America and Cuba. South Bend, Indiana: Notre Dame University Press; 1944.
201. Cooper EL. Med J Aust 1942;1:635.
202. Corkill NL. Ann Trop Med Parasitol 1948;42:230.
203. Correa P, Baylet RJ, Parsons L. Bull Soc Med Afr Noire Lang Franc 1964;9:215.
204. Coryllos J, Perakis M. Bull Mém Soc Hôp Paris 1918;29:513.
205. Costiniu J. Presse Med 1920;28:453.
206. Cragg FW. Indian J Med Res 1922a;10:78.
207. Cragg FW. Trans R Soc Trop Med Hyg 1922b;15:236.
208. Culpepper GH. J Econ Entomol 1946a;39:472.
209. Culpepper GH. J Econ Entomol 1946b;39:660.
210. Cumberland MC, Turner TB. Am J Syph 1947;31:485.
211. Cunningham J. Trans R Soc Trop Med Hyg 1925;19:11.
212. Cunningham J, Fraser AGL. Indian J Med Res 1935;22:595.
213. Cunnigham J, Theodore JH, Fraser AGL. Indian J Med Res 1934;22:105.
214. Daels H. Arch Hyg 1910;72:257.
215. Davidson Sir S. Principles and Practice of Medicine, 5th ed. Baltimore, Maryland: Williams & Wilkins Co; 1960.
216. Davis GE. Public Health Rep 1939;54:1721.
217. Davis GE. Public Health Rep 1941a;56:1799.
218. Davis GE. Public Health Rep 1941b;56:2010.
219. Davis GE. Am Assoc Adv Sci Symposium No. 18 1942a;41.
220. Davis GE. Am Assoc Adv Sci Symposium No. 18 1942b;67.
221. Davis GE. Public Health Rep 1943;58:839.
222. Davis GE. Ann Rev Microbiol 1948;2:305.
223. Davis GE. Exp Parasitol 1952a;1:406.
224. Davis GE. J Parasitol 1952b;38:473.
225. Davis GE. Am J Hyg 1956;63:13.
226. Davis GE, Burgdorfer W. Exp Parasitol 1955;4:100.
227. Davis GE, Mavros AJ. Bull Soc Pathol Exot 1955;48:698.
228. Davis GE, Mazzotti L. J Parasitol 1953;39:663.
229. Delameter ED. Trans NY Acad Sci 1952;14:199.
230. Delanoë P. C R Acad Sci 1929;189:398.

231. Delanoë P. C R Acad Sci 1930;191:148 1.
232. Delanoë P. C R Acad Sci 1931;193:450.
233. Delanoë P. Bull Soc Pathol Exot 1933;26:1249.
234. Delpy LP. Bull Soc Pathol Exot 1949;42:147.
235. Delpy LP, Rafyi A. Ann Parasitol Hum Compar 1939;17:45.
236. Delpy LP, Rafyi A, Maghami RD. Bull Soc Pathol Exot 1948;41:136
237. Desportes C, Campana Y. Ann Parasitol Hum Compar 1946;21:74.
238. Diaz Ferrón E. Rev Clin Esp 1957;64:97.
239. Dickie CW, Barrera J. Avian Dis 1964;8:191.
240. D'Ignazio C, Codelconcinci E. Boll Soc Ital Med Ig Trop Sez Eritrea 1946;6:237.
241. Dirk Van Peenen PF. East Afr Med J 1963;40:83.
242. Dixon KC. J R Army Med Corps 1943;81:193.
243. Dobell C. Arch Protistenkunde 1912;26:119.
244. Drake–Brockman RE. Trans R Soc Trop Med Hyg 1915;8:201.
245. Dschunkowsky E. Dtsch Med Wochenschr 1913;39:419.
246. Du SD. Chinese Med J 1931;45:657.
247. Dubois A. Ann Soc Belg Méd Trop 1949;29:15.
248, Donn LH, Clark HC. Am J Trop Med 1943;13:201.
249. Durieux C, Boiron H. Bull Soc Pathol Exot 1950;43:403.
250. Dutton JE, Todd JL. Br Med J 1905;ii:1259.
251. Eddy GW. J Econ Entomol 1952;45:1043.
252. Eidmann E, Poespodihardjo S, Vinke W. Z Tropenmed Parasit 1959;10:442.
253. Eisenberg S, Gunders AE, Cohen AM. Trans R Soc Trop Med Hyg 1968;62:679.
254. El Dardiry EH. Techn Sci Soc Bull Egypt 1945;243:1.
255. El Ramly AH. J Egypt Public Health Assoc 1946;21:125.
256. Elsdon–Dew R. Nature 1943;152:565.
257. Enigk K, Grittner I. Z Parasitenk1953;16:56.
258. Erocli N, Bobalik G, Stubbs R. In: Antibiotics Annual, Medical Encyclopedia. New York, 1956-57;601.
259. Ercoli N, Lafferty LC. Proc Soc Exp Biol Med 1944;57:4.
260. Falcone G. Arch Ital Sci Med Trop Parasitol 1951;37:1031.
261. Favorova LA, Chernysheva TF, Beshcheva NI, Mikhalov AK, Trifonov VI. Med Parazitol (Mosk) 1967;36:319.
262. Felsenfeld O. Acto Med Latina 1932;1:36.
263. Felsenfeld O. Rev Hig Valencia 1935;28:291.
264. Felsenfeld O. Bacteriol Rev 1965;29:46.
265. Felsenfeld O, Decker WJ, Wohlhieter JA, Rafyi A. J Immunol 1965;94:805.
266. Felsenfeld O, Volini IF, Ishihara SJ, Bachman MC, Young VM. J Lab Clin Med 1950;35:428.
267. Felsenfeld O, Volini IF, Young VM, Ishihara SJ. Am J Trop Med 1950;30:499.
268. Felsenfeld O, Wolf RW. Acta Trop 1969;26:198.
269. Fendall NRE, Grounds JG. J Trop Med Hyg 1965;68:134.
270. Feng LC, Chung HL. Chin Med J 1936;50:1185.
271. Feng LC, Chung HL. Acta Conventus Tertii Tropics atque Malariae Morbus 1938;1:438.
272. Fenyvessy BV, Scheff G. Biochem Ztschr 1930;211:206.
273. Fisher FP, Fischle V. Biochem Ztschr 1933;267:403.
274. Fisher WM. Am Assoc Adv Sci Symposium No. 18 1942;15.
275. Fletcher JP, Plaut CB. Oral Surg Oral Med Oral Pathol 1966;22:729.
276. Forteza Bover J, Garriguez Orellana A, Marco Orts T. Rev Sanid Hig Publica (Madr) 1949;23:3.
277. Franchini G. Arch Ital Sci Med Colon 1930;11:449.
278. Francis E. Public Health Rep 1938;53:2220.
279. Francis E. Am Assoc Adv Sci Symposium No. 18 1942;85.
280. Fränkel L. Virchow's Arch Pathol Anat Physiol 1912;18:97.
281. Friedemann V. Physiol Rev 1942;22:125.
282. Fry AG. Indian Med Gaz 1920;55:2.
283. Fuchs PC, Oyama AA. JAMA 1969;208:690.
284. Fülleborn F, Mayer M. Arch Schiff Trop Hyg 1908;12:31.
285. Fulton JD, Smith PC. Biochem J 1960;76:491.
286. Gaillard H, Lapièrre J, Coste M. Ann Parasitol Hum Compar 1963;38:1.
287. Galliard H, Lapièrre J, Rousset JJ. Pathol Biol 1960;8:77.
288. Galloway IA. CR Soc Biol 1925;93:1074.
289. Galun R, Warburg M, Avidi A. Entomol Exp Appl 1967;10:143.
290. Galouzo IG. Argasid Ticks. Acad Sci Kazakh SSR, Alma-Ata,Translat. USNMRU #3; 1957.
291. Gambles RM, Coghill NF. Ann Trop Med Parasitol 1948;42:288.
292. Garnham PCC. East Afr Med J 1936;73:50.
293. Garnham PCC. East Afr Med J 1947;24:47.
294. Garnham PCC. Parasitology 1950;40:328.
295. Garnham PCC. J Trop Med Hyg 1958;61:92.
296. Garnham PCC, Davies CW, Heisch RB, Timms GL. Trans R Soc Trop Med Hyg 1947;41:141.
297. Gaud M, Khalil M Bey, Vaucel M. Bull World Health Organ 1947-1948;1:93.
298. Gaud M, Morgan MT. Bull World Health Organ 1947-1948;1:69.
299. Gefel A, Rubenow R. Harefuah 1953;44:263.
300. Geigy R Atti 3o Congr Intern Ig Med Mediter, Palermo 1951;56.
301. Geigy R. Rev Suisse Zool 1953a;60:439.
302. Geigy R. Schweiz Ztschr Pathol Bakt 1953b;16:821.
303. Geigy R. In: Infectious Diseases of Man and Animals, 1968;2:175.
304. Geigy R, Aeschlimann A. Ztschr Tropenmed Parasitol 1957;8:96.
305. Geigy R, Aeschlimann A. Rev Suisse Zool 1965;72.87.
306. Geigy R, Burgdorfer W. Rev Suisse Zool 1949;56:334.
307. Geigy R, Burgdorfer W. Acta Trop 1951;8:151.
308. Geigy R, Herbig A. Erreger und Überträger Tropischer Krankheiten. Verlag fur Recht und Gesellschaft, Basel. Acta Trop. 1955;6(suppl).
309. Geigy R, Mooser H. J Trop Med Hyg 1955;58:199.
310. Geigy R, Sarasin G. Pathol Microbiol 1960;24:93.
311. Geigy R, Sarasin G. Acta Trop 1961a;78:359.
312. Geigy R, Sarasin G. Pathol Mikrobiol 1961b;24(suppl):93.
313. Geigy R, Wagner O, Aeschlimann A. Acta Trop 1954;11:81.
314. Geiman QM. Ann Rev Microbiol 1952;6:299.
315. Gelman AC. In: May JM, ed. Studies in Disease Ecology. New York: Haffner Publishing Co; 1961.
316. Gill CA. Indian J Med Res 1922;9:747.
317. Gimeno de Sande A. Rev Sanid Hig Publica 1954;28:342.
318. Ginger CD. Nature 1963;199:159.
319. Goldberg HJ. J Oral Ther 1966;2:451.
320. Gönnert R, Mudrow–Reichenaw L. Ztschr Tropenmed Parasitol 1956;7:369.
321. Graham M. Texas State J Med 1931;27:226.
322. Gray JDA. Ann Trop Med Parasitol 1929;23:241.
323. Greaves FC, Gezon HM, Lind Alston WF. US Naval Med Bull 1945;45:1029.
324. Greiner J. Bull Soc Pathol Exot 1921;14:144.
325. Gross WM, Ball MR. Am J Vet Res 1964;25:1734.
326. Grothusen J. Arch Schiff Tropenhyg 1920;24:50.
327. Grim H. Ztschr Hyg Infektkrk 1950;131:198.
328. Guggenheim K, Buechler–Czaczkes E, Halevi S. J Infect Dis 1951;89:105.
329. Guggenheim K, Halevi S. J Infect Dis 1952;90:190.
330. Guzzon V, Ercoli N. Boll Ist Seroterap Milano 1951;30:543.
331. Haberkorn A. Ztschr Tropenmed Parasit 1963;14:209.
332. Haddad C, Sheiban A, Budeir R. J Palestine Arab Med Assoc 1946;2:8.
333. Halawani A. J Egypt Public Health Assoc 1946;21:183.
334. Hallauer C, Kuhn H. Ztschr Hyg Infektkrk 1940;122:406.
335. Hamilton JB. Br J Ophthalmol 1943;27:68.
336. Hanson AW, Cannefax GR. J Bacteriol 1964;88:811.
337. Harold CTH. J R Army Med Corps 1922;38:398.
338. Hawkins F. J Trop Med Hyg 1941;44:104.
339. Heilman FR. Proc Staff Meet Mayo Clin 1948;23:569.
340. Heisch RB. East Afr Med J 1947;24:3.
341. Heisch RB. Br Med J 1949;i:17.
342. Heisch RB. Ann Trop Med Parasitol 1950a;44:260.

343. Heisch RB. East Afr Med J 1950b;27:1.
344. Heisch RB. East Afr Med J 1952;29:327.
345. Heisch RB. Parasitology 1953;43:133.
346. Heisch RB. Trans R Soc Trop Med Hyg 1955a;49:92.
347. Heisch RB. Bull Soc Pathol Exot 1955b;48:322.
348. Heisch RB, Chamsa M, Seydian B, Harvey AEC. Bull Soc Pathol Exot 1957;50:735.
349. Heisch RB, Garnham PCC. Parasitology 1948;38:247.
350. Heisch RB, Grainiger WE. Ann Trop Med Parasitol 1950;44:153.
351. Heisch RB, Harvey AEC. East Afr Med J 1952;29:25.
352. Heisch RB, Harvey AEC. Trans R Soc Trop Med Hyg 1953;47:239.
353. Heisch RB, Harvey AEC. Parasitology 1962a;52:77.
354. Heisch RB, Harvey, AEC. East Afr Med J 1962b;39:609.
355. Heisch RB, Sparrow H, Harvey AEC. Bull Soc Pathol Exot 1960;53:140.
356. Hemingway WF, Hemingway RW, Arneson VK. Northwest Med 1940;39:362.
357. Hermant D. Bull Soc Méd Chir Indochine 1912;3:418.
358. Herms WB, Wheeler CM. J Parasitol 1936;22:276.
359. Himmelweit F. Ztschr Hyg Infektkrk 1933;115:710.
360. Hindemarsh WL. New South Wales Dept Agr Vet Res Rep 1937;7:69.
361. Hindle E. Parasitology 1911;4:183.
362. Hindle E. Proc Cambridge Philos Soc 1912;16(part 6):457.
363. Hindle E. In: A System of Bacteriology in Relation to Medicine. Med Res Council H M Stat Off London 1931a;8:101.
364. Hindle E. In: A System of Bacteriology in Relation to Medicine. Med Res Council H M Stat Off London 1931b;8:147.
365. Hindle E. Trop Dis Bull 1935;32:309.
366. Hirschboeck MM. Am J Trop Med Hyg 1954;3:712.
367. Hjelle A. Nature 1966;212:856.
368. Hoffman HA, Jackson TA. J Am Vet Med Assoc 1946;109:481.
369. Hoffman HA, Jackson TA, Rucker JC. J Am Vet Med Assoc 1946;108:329.
370. Holmes JWE. J R Sanit Inst 1953;73:262.
371. Hoogstraal H. African Ixoidea I. Ticks of the Sudan. US Navy Dept Res Rept No. NM005050.20.07. Washington, DC, 1956.
372. Horrenberger R. Arch Inst Pasteur Alger 1954;32:18.
373. Horrenberger R. Arch Inst Pasteur Alger 1955;33:258.
374. Horsfall WR. Medical Entomology. New York, NY: Ronald Press Co.; 1962.
375. Huang VD. Zool Zh 1960;39:595.
376. Hungerford TG, Hart L. Agric Gaz New South Wales 1938;48:591.
377. Hunter W. Proc R Soc Med 1919;13:129.
378. Ingraham HS, Lapenta RG. US Naval Med Bull 1946;46:1718.
379. International Sanitary Regulations, 3rd ed. World Health Organization, Geneva, Switzerland, 1967.
380. Ishii N, Smimizu S. Japan J Exp Med 1941;19:5.
381. Ishii N, Shimizu S, Tsuda K. Japan J Med Exp Med 1941;19:5.
382. Jahnel F. Ztschr Immunfschg 1938;92:253.
383. Jancsó N. Cbl Bact Abt I Orig 1918;81:457.
384. Jellison WL. Public Health Rep 1940;55:206.
385. Jepson WF. Nature 1947;160:874.
386. Johnstone HG. Am Assoc Adv Sci Symposium No. 18, 1942;35.
387. Jouveau–Dubreuhil H. Bull Soc Pathol Exot 1919;12:621.
388. Jouveau–Dubreuhil J. Bull Soc Pathol Exot 1920;13:38.
389. Joyeux S, Sautet J. Bull Soc Pathol Exot 1938;31:279.
390. Juárez N, Fernández S. Rev Sanid Hig Publica 1954;28:133.
391. Judge DM, Perine LL. Proc 8th Congress Trop Med Malar 1968;894.
392. Jukes AM. Indian Med Gaz 1912;47:476.
393. Kalajew AW. G Batteriol Virol Immunol 1931;7:184.
394. Kalra SL, Rao KNA. Indian J Med Res 1951;39:319.
395. Kamal AM, Anwar M, Abdel Messih A, Kolta Z. J Egypt Public Health Assoc 1947;1:1.
396. Kapur HR. Indian J Vet Sci Anim Husb 1940;10:354.
397. Karwacki L, Krakowska Z. Lekarz Wojskowy 1921;2:27.
398. Kassirsky JA. Arch Schiff Trop Hyg 1933;37:380.
399. Kaupp BF. Poultry Diseases. Chicago, IL: Alexander Eger Co.; 1917.
400. Kawamura H. Zbl Bakt Parasit Abt I Orig 1931;120:59.
401. Kawata T. Yonago Acta Med 1957;2:142.
402. Kawata T. Japan J Microbiol 1961;5:203.
403. Kawata T, Inoue T. Japan J Microbiol 1964;8:49.
404. Kemp HA, Haam EV, Fisher WM, Evans HL. Am Assoc Adv Sci Symposium No. 18, 1942;117.
405. Kemp HA, Moursund WH, Wright HF. Am J Trop Med 1934a;14:159.
406. Kemp HA, Moursund WH, Wright HE. Am J Trop Med 1934b;14:163.
407. Kemp HA, Moursund WH, Wright HE. Am J Trop Med 1934c;14:479.
408. Kemp HA, Moursund WH, Wright HE. Am J Trop Med 1935;15:495.
409. Kervran P. Bull Soc Pathol Exot 1947;40:152.
410. Kirk R. Ann Trop Med Parasitol 1938;32:125.
411. Kirk R. Ann Trop Med Parasitol 1939;33:125.
412. Kley D, Ercoli N. Experientia 1950;6:153.
413. Kligler IJ, Hermani D, Perek M. J Compar Pathol 1938;51:206.
414. Kligler IJ, Robertson OH. J Exp Med 1922;35:303.
415. Knowles R, DasGupta BM, Basu BC. Indian J Med Res 1932;22:1.
416. Knox JD. J R Coll Gener Pract 1968;16:23.
417. Koch R. Dtsch Med Wochenschr 1905;31:1865.
418. Koch R. Klin Wochenschr 1906;43:185.
418a. Kolev M. Vet Med Nauki 1967;4:97.
419. Konitzer L. Acta Med Orient 1949;8:48.
420. Krakowski I, Edelstein A. Harefuah 1949;36:101.
421. Kritschewski IL, Dvolaitskaya–Barischewa KM. Zbl Bakt Parasit Abt I Orig 1931;121:421.
422. Kritschewski IL, Sinjuschima MN. Krankheitsforschung 1931;9:139.
423. Krichevsky MF, Hampp EG. J Dent Res 1966;45:165.
424. Kröber F. Arch Schiff Trop Hyg 1936;40:160.
425. Kroó HV. Ztschr Pathol Bacteriol 1949;12:60.
426. Krylova DP. Med Parazitol 1963;6:659.
427. Kudicke R, Feldt A, Collier WA. Ztschr Hyg Infektkrk 1924;102:135.
428. Kudicke R, Kudicke H, Grammel H, Linhoffer A. Ztschr Hyg Infektkrk 1953;137:13.
429. L'Abbate G, Mannino S. Arch Ital Sci Med Colon Paras 1938;19:486.
430. Lamoureaux A. Bull Soc Pathol Exot 1913;6:146.
431. Landauer E. Ann Inst Pasteur 1931;47:667.
432. Lanzo A, Tresca G. Arch Ital Sci Med Trop 1961;42:434.
433. Lapierre J, Gaillard H, Roussett JJ. C R Soc Biol 1964;158:1047.
434. Lapierre J, Larivière M, Rousset JJ.Bull Soc Pathol Exot 1958;51:173.
435. Lapierre J, Rousset JJ, Picot M. C R Soc Biol 1959;153:1718.
436. Larivière M, Hocquet P, Camerlynck P. Bull Soc Méd Afr Noire Lang Franc 1960;1:17.
437. Leboeuf A, Gambier A. Bull Soc Pathol Exot 1919;12:497.
438. Leeds AD. Parasitology 1946;37:172.
439. LeGac J. Ann Méd Pharm Colon 1931;29:148.
440. Legge RT. Calif Western Med 1933;38:370.
441. Leifson E. J Bacteriol 1950;60:678.
442. Leishman WB. Lancet 1920;i:1237.
443. León LA, Leon BC. Rev Kuba 1947;3:145.
444. Leonova NA. Med Parazitol 1945;14:79.
445. Lesbouyries G. La Pathologie des Oiseaux. Vigot Frères, Paris, 1941.
446. Levaditi JC, Balouet G, Juminer B, Corcos A. Bull Soc Pathol Exot 1966;59:310.
447. Levaditi C, Henry–Eveno J. C R Acad Sci 1953;236:339.
448. Levaditi C, Vaisman A. C R Acad Sci 1947;225:769.
449. Levaditi C, Vaisman A, Hamelin A. Ann Inst Pasteur 1952a;83:256.

450. Levaditi C, Vaisman A, Hamelin A. Ann Inst Pasteur 1952b;83:437.
451. Levine BS. Public Health Rep 1952;67:253.
452. Li YP. Ann Parasitol Hum Compar 1936;14:76.
453. Lipinski W. Pol Tyg Lek 1949;5:1465.
454. Lodewyckx A. Ann Soc Belg Med Trop 1938;18:487.
455. Loewy J. Berlin Klin Wochenschr 1919;14:341.
456. Lofgren R, Soule MH. J Bacteriol 1945a;50:305.
457. Lofgren R, Soule MH. J Bacteriol 1945b;50:679.
458. Longanecker DS. Am J Trop Med 1951;31:373.
459. Loomis EC. Am J Vet Res 1953;14:612.
460. López Portillo S. Rev Inst Salubr Enferm Trop 1942;3:41.
461. Lovett WCD. Trans R Soc Trop Med Hyg 1956;50:157.
462. Mackie FP. Br Med J 1920;1:380.
463. Maestrone G. Nature 1964;197:409.
464. Magee GR. Am Assoc Adv Sci Symposium No. 18, 1942;106.
465. Mailloux M. Arch Inst Pasteur Alger 1962;40:344.
466. Malberger E. J Periodontal Res 1967;2:154.
467. Manson JK, Thornton LHD. J R Army Med Corps 1919;33:97.
468. Manteufel P, Dressler I. Zbl Bakt Abt I Orig 1933;130:188.
469. Marques A. Ann Inst Med Trop Lisbon 1943;1:187.
470. Martinez Baez M, Villasana H. Rev Inst Salubr Enferm Trop 1945;6:185.
471. Martini E, Rimpau W. In:Rodenwalt E. Weltseuchensatlas Falk Verla,. Hamburg, 1952.
472. Marchoux E, Salimbeni A. Ann Inst Pasteur 1903;17:569.
473. Margolis A. Beitr Klin Infektkrk 1919;7:254.
474. Marinkelle CJ, Grose ES. Nature 1968;218:487.
475. Maruashvilli GM. Med Parazitol 1945;14:24.
476. Más de Ayala I. Méd Paises Cálidos 1931;4:369.
477. Mathey WJ Jr, Siddle PJ. J Am Vet Med Assoc 1955;86:122.
478. Mathis C. Bull Acad Méd Paris 1931;106:188.
479. Mathis C, Durieux C. Bull Soc Pathol Exot 1931;24:150.
480. Mathis C, Durieux C, Advier M. Bull Soc Pathol Exot 1933;26:1094.
481. Mathis C, Durieux C. Bull Acad Méd Paris 1934;111:528.
482. Mayer A. Ztschr Klin Med 1922;90:141.
483. Mazzotti L. Rev Inst Salubr Enferm Trop 1942a;3:213.
484. Mazzotti L. Rev Inst Salubr Enferm Trop 1942b;3:297.
485. Mazzotti L. Am J Hyg 1943;38:203.
486. McKee RW, Geiman QM. Feder Proc 1950;9:201.
487. McKercher DG. J Bacteriol 1950;59:446.
488. McNeil E, Hinshaw WR, Kissling RE. J Bacteriol 1948;57:191.
489. Meador CN. Colorado Med 1915;12:365.
490. Meleney HE. J Exp Med 1928;48:65.
491. Merliss R. Med Arts Sci 1952;6:44.
492. Mersekey C. Clin Proc Cape Town 1947;6:111.
493. Meyer PA, Hunter EF. J Bacteriol 1967;39:784.
494. Miller PBM. Pacific Med Surg J 1874-1875;17:370.
495. Millous J. Bull Soc Méd Chir Indochine 1913;4:14.
496. Mishchenko NK. Zool Zh 1960;39:424.
497. Moise RMR. Ann Med Naval Colon 1938;44:315.
498. Mölbert E. Ztschr Hyg Infektkrk 1956;142:103.
499. Mooser H. Ztschr Tropenmed Parasitol 1958a;9:93.
500. Mooser H. Ergebn Mikrobiol 1958b;31:184.
501. Mooser H. Acta Trop 1963;20:369.
502. Mooser H, Weyer F. Ztschr Tropenmed Parasitol 1954;5:28.
503. Moreno Berdugo J, Infante Gómez A. Med Colon 1945;6:336.
504. Moroder J. Arch Schiff Trop Hyg 1929;33:603.
505. Morrison SK, Parsons L. JAMA 1941;116:220.
506. Moskwin IA. Ztschr Parasitol 1929;2:73,
507. Moursund WH. Am Assoc Adv Sci Symposium No. 18, 1942;1.
508. Mouzels P, Xuang Mai N. Bull Sci Méd Chir Indochine 1912;3:427.
509. Mühlens P. Chinese Med J 1933;47:1384.
510. Muñoz Cosin F. Med Colon 1953;22:457.
511. Muñoz Cosin F. Med Trop 1960;35:173.
512. Murrell TW. Arch Dermatol 1939;39:667.
513. Nagano L. Tokyo Igakai Zasshi 1941;3:21.
514. Nájera Angulo L. Bol Réal Soc Españ Hist Natur 1943;41:527.
515. Nájera Angulo L. Bol Réal Soc Españ Hist Natur 1945;43:217.
516. Narain S, Kalra SL. Indian Med Gaz 1950;85:87.
517. Néel R, Payet M, Gonnet C. Bull Soc Pathol Exot 1949;42:384.
518. Nevin TA, Guest WJ. J Bacteriol 1967;94:1388.
519. Newcomb C. Indian Med Gaz 1920;55:208.
520. Nicolle C, Anderson C. Arch Inst Pasteur Tunis 1926;15:197.
521. Nicolle C, Anderson C. Bull Inst Pasteur 1927a;25:657.
522. Nicolle C, Anderson C. Arch Inst Pasteur Tunis 1927b;16:123.
523. Nicolle C, Anderson C. C R Acad Sci 1929a;189:817.
524. Nicolle C, Anderson C. Acta Med Scandin 1929b;70:392.
525. Nicolle C, Anderson C. Arch Inst Pasteur Tunis 1929c;18:268.
526. Nicolle C, Anderson C. Arch Inst Pasteur Tunis 1930;19:469.
527. Nicolle C, Anderson C. C R Acad Sci 1932;194:333.
528. Nicolle C, Anderson C, Colas–Belcour J. C R Acad Sci 1929;189:224.
529. Nicolle C, Anderson C, Colas–Belcour J. Arch Inst Pasteur Tunis 1930;19:133.
530. Nicolle, C., Anderson, C., and Hornus, P. C R Acad Sci 1929;188:1211.
531. Nicolle C, Blaizot L. Bull Soc Pathol Exot 1912a;5:472.
532. Nicolle C, Blaizot L. Arch Inst Pasteur Tunis 1912b;1:201.
533. Nicolle C, Blaizot L. Bull Soc Pathol Exot 1913;6:107.
534. Nicolle C, Blaizot L, Conseil E. C R Acad Sci 1912a;154:1636.
535. Nicolle C, Blaizot L, Conseil E. C R Acad Sci 1912b;155:481.
536. Nicolle C, Blaizot L, Conseil E. Bull Soc Path Exot 1913;6:106.
537. Nicolle C, Lebrailly C. C R Acad Sci 1919;169:934.
538. Nicolle C, Lebrailly C. Arch Inst Pasteur Tunis 1920;11:131.
539. Nieschulz OV, Bos A. Zbl Bakt Abt I Orig 1940;145:258.
540. Nikitina RE. Sbor Trud Vsech Nauch Bolez Ptits 1965a;1:164.
541. Nikitina RE. Zool Zh 1965b;44:294.
542. Nixon A. Lancet 1921;i:432.
543. Noble RE, Noble CA. Parasitology, 2nd ed. Philadelphia, PA: Lea and Febiger; 1964
544. Noguchi H. J Exp Med 1912a;16:199.
545. Noguchi H. Münch Med Wochenschr 1912b;59:1937.
546. Nohira A. Japan Med World 1929;9:83.
547. Novy FG, Knapp RE. J Infect Dis 1906;3:291.
548. Nuttall GHF. Parasitology 1913;5:262.
549. Oag RK. J Pathol Bacteriol 1939;49:339.
550. Oag RK. J Pathol Bacteriol 1940;51:127.
551. Oettinger J, Halbreich J. Münch Med Wochenschr 1922;69:778.
552. Omar MES. J Egypt Public Health Assoc 1946;21:195.
553. Ombati DG, Ojiambo HP. East Afr Med J 1968;45:630.
554. Omori N. Taiwan Igakai Zasshii 1939;38:899.
555. Ordman D. South Afr Med J 1939;13:491.
556. Ordman D. South Afr Med J 1955;29:518.
557. Ordman D, Jones FR. South Afr Med J 1940;14:81.
558. Osorno Mesa S. Rev Fac Nac Agronom Medellin 1942;16/17:1.
559. Packchanian AH. Texas Rep Biol Med 1950;8:78.
560. Palmer JH, Crawford DJM. J Can Med Assoc 1933;28:643.
561. Pampana EJ. Arch Ital Sci Med Colon 1931;12:257.
562. Parry EHO, Bryceson ADM, Leihead CS. Lancet 1967;i:81.
563. Pavolvskii EN. Trudy Soviet Izuch Proizvod Turkmenia 1932;2:79.
564. Pavlovskii EN. Prob Region Parasitol 1939;3:19.
565. Pavlovskii EN. C R Acad Sci USSR 1943;39:286
566. Pavlovskii EN. Med Parasitol 1945;14:56.
567. Pavlovskii EN, Kuzima LA. Med Parazitol 1945;14:66.
568. Pavlovskii EN, Skrynnik AN. Zool Zh 1945;24:161.
569. Pavlovskii EN, Skrynnik AN. Dokl Akad Nauk USSR 1951;78:1069.
570. Petrilla A, Rudnay O. Népegészségügy 1949;30:439.
571. Petrishcheva PA. Med Parazitol 1961;30:439.
572. Pfister R. Bull Soc Pathol Exot 1949;42:547.
573. Pifano F. Rev Sanid Asist Soc Caracas 1941;6:787.
574. Pillot J. Biol Med (Paris) 1966;55:343.
575. Pillot J, Dupouey P, Ryter A. Ann Inst Pasteur 1954;107:489, 663.
576. Pillot J, Ryter A. Ann Inst Pasteur 1965;108:791.
577. Pino–Pou R. Gac Méd Caracas 1921;28:111.
578. Pinto MR. Arq Inst Bacteriol Camara Pestana 1945;9:224.
579. Pirot R, Bourgain M. Bull Soc Pathol Exot 1945a;38:12.

580. Pirot R, Bourgain M. Bull Soc Pathol Exot 1945b;38:88.
581. Pirot R, Bourgain M. Bull Soc Pathol Exot 1945a;38:90.
582. Plaut F, Steiner G. Arch Schiff Trop Hyg 1920a;24:33.
583. Plaut F, Steiner G. Dtsch Med Wochenschr 1920b;46:1101.
584. Popow PP, Achundow IA. Arch Schiff Trop Hyg 1936;40:289.
585. Popow PP, Achundow IA. Med Parazitol 1940;9:255.
586. Pospelova–Shtrom MV. Med Parazitol 1940;9:618.
587. Pospelova–Shtrom MV. Proc 8th Int Congress Trop Med Malar 1968;888.
588. Prado E del. Crónica Méd Lima 1919;36:408.
589. Prado E del. Ann Fac Méd Lima 1920;3:26,134.
590. Quinn CE, Perkins ES. J Trop Med Hyg 1946;49:30.
591. Rafyi A. Arch Inst Hessarek 1946a;2:37.
592. Rafyi A. Arch Inst Hessarek1946b;4:49 and Sem Hôp Paris 1946b;23:76.
593. Rafyi A, Felsenfeld O, Dupont JR, Maghami G. Ann Parasitol Hum Compar 1965;40:63 1.
594. Rafyi A, Maghami GR. Bull Soc Pathol Exot 1949;42:215.
595. Rahaman AH. J Egypt Public Health Assoc 1946;21:125.
596. Ranque J. Transfusion (Paris) 1963;6:163.
597. Ranque J. Méd Trop (Marseille) 1968;27:519.
598. Ranque J, Depieds R, Fauré A. Bull Soc Pathol Exot 1957;50:360.
599. Ranque J, Quilici M, Assadourian Y. Proc 8th Int Congress Trop Med Malar 1968;2:893.
600. Rao KNA, Kalra SL. Indian J Med Res 1949;37:385.
601. Reddy VM, Ramachandran PK, Ramachandran S. Indian J Vet Sci Anim Husb 1966;36:1.
602. Remlinger P, Bailly J. C R Soc Biol 1929;102:741.
603. Riding D, McDowell TW. Trans R Soc Trop Med Hyg 1927;20:524.
604. Roaf HE. Br J Exp Pathol 1922;3:59.
605. Robertson A. J Trop Med Hyg 1935;38:237.
606. Robertson RC. Chinese Med J 1932;20:524.
607. Robinson P. Br Med J 1942;ii:216.
608. Robinson SP. Ann Trop Med Parasitol 1943;37:38.
609. Rodhain J, Bergh L van den. Ann Soc Belg Med Trop 1943;23:141.
610. Rodino N. G Med Milit 1922;70:90.
611. Rosenholz HP. Cbl Bact Abt I Orig 1927;102:179.
612. Ross PH. Nairobi Lab Public Health Rep 1912;2(part 2):6.
613. Ross PH, Milne AD. Br Med J 1904;ii:1453.
614. Roy SC. Indian Med Gaz 1920;56:320.
615. Rubinstein PL, Kapusto ML. Ztschr Immunfschg Exp Ther 1931;72:309.
617. Russell H. Trans R Soc Trop Med Hyg 1932;26:259.
618. Russel H. West Afr Med J 1933;6:36.
619. Russell H. Trans R Soc Trop Med Hyg 1936;30:179.
620. Sabalette R, Dominguez M, Iglesias R. Med Colon (Madrid) 1947;9:207.
621. Saglam T. Türk Tip Cemiyeti Mekmuasi 1947;13:36.
622. Sarasin G. Acta Trop 1959;16:218.
623. Saurinov VR, Delamater ED. Am J Syph 1952;36:352.
624. Sautet J. Marseille Méd 1937;74:273.
625. Sautet J. Arch Inst Pasteur Alger 1941;19:240.
626. Scheff G. Zbl Bakt Parasitol Abt I Orig 1935;134:35.
627. Scheff GJ, Kutner FR. Experientia 1959;15:342.
628. Schilling V. Beiheft Arch Schiff Trop Hyg 1921;25:5.
629. Schofield TPC, Talbot JM, Bryceson ADM, Parry EHO. Lancet 1968;ii:58.
630. Schuhardt VT. Am Assoc Adv Sci Symposium No. 18, 1942;58.
631. Schuhardt VT. Ann N Y Acad Sci 1952;55:1209.
632. Schuhardt VT, Wilkerson M. J Bacteriol 1951;62:215.
633. Schwetz J. Ann Soc Belg Med Trop 1953;23:219.
634. Scott HH. A History of Tropical Medicine, 2. Baltimore, MD: Williams & Wilkins Co.; 1942:781.
635. Scott RB. Lancet 1944;ii:436.
636. Selwyn–Clarge PS, LeFanu GH, Ingram A. Ann Trop Med Parasitol 1923;17:389.
637. Sergent A. C R Acad Sci 1933;197:717.
638. Sergent A. C R Soc Biol 1936;14:1520.
639. Sergent A. Arch Inst Pasteur 1938;61:217.
640. Sergent E. Ann Inst Pasteur Alger 1945;23:245.
640a. Sergent E. Ztschr Tropenmed Parasitol 1957;3:242.
641. Sergent E, Foley H. Bull Soc Pathol Exot 1908;1:174.
642. Sergent E, Foley H. Bull Soc Pathol Exot 1921;14:632.
643. Sergent E, Poncet A. Arch Inst Pasteur Alger 1961;39:109.
644. Serstnev E. Higijena 1953;5:106.
645. Shrimpton EAG. Chinese Med J 1936;(suppl I):312.
646. Sibilia D. Policlinico 1937;44:722.
647. Simmons JS. In: Cecil RL. Textbook of Medicine, 9th ed. New York, NY: Saunders & Co.; 1965
648. Simons H. Ann Parasitol Hum Compar 1939;17:62.
649. Skinner JE, Trimble CG, Cheng CG. Chinese Med J 1919;33:210.
650. Skrynnik AN. Parazitologiia 1968;2:3.
651. Slavina NS. Med Parazitol 1944;13:85.
652. Smith L, Brown TG. California Med 1969;101:322.
653. Smith PJC. Biochem J 1960a;76:500.
654. Smith PJC. Biochem J 1960b;76:508.
655. Sofiev MS. Med Parazitol 1941;10:267.
656. Sofiev MS, Leitman MZ. Med Parazitol 1946;15:81.
657. Sofiev MS, Leonova NA. Med Parazitol 1945;14:60.
658. Soule MH. Am Assoc Adv Sci Symposium No. 18, 1942;53.
659. Southern PM Jr, Sanford JP. Medicine 1968;48:129.
660. Sparrow H. Arch Inst Pasteur Tunis 1955a;32:25.
661. Sparrow H. C R Acad Sci 1955b;241:1636.
662. Sparrow H. Bull Soc Pathol Exot 1956a;49:630.
663. Sparrow H. Arch Inst Pasteur Tunis 1956b;33:163.
664. Sparrow H. Bull World Health Organ 1958;19:673.
665. Sparrow H. Proc 6th Int Congress Trop Med Malar 1959;4:484.
666. Sreenivasan MK, Sankaranarayan NS. Indian Vet J 1945;21:325.
667. Stavitsky AB. Bacteriol Rev 1948;12:203.
668. Stein GJ. J Exp Med 1944;79:115.
669. Sterling–Okunewski S. Cbl Bact Abt I Orig 1919;82:456.
670. Stuart G. Epidem Inform Bull UNRRA 1945;1:453.
671. Suchanek J, Ciecierski L, Lawrynowycz R. Pol Tyg Lek 1957;22:1103.
672. Sudley EW. Bull Soc Pathol Exot 1920;13:63.
673. Swain RHA. J Pathol Bacteriol 1955;69:117.
674. Taft C, Pike JB. JAMA 1945;129:1002.
675. Talice RV. Ann Parasitol Hum Compar 1929;7:177.
677. Tesdale C. East Afr Med J 1952;29:138,
678. Tesdale C. East Afr Med J 1965;52:529.
679. Teravskii IK. Zool Zh 1966;45:371.
680. Thayer KH. Southwest Med 1940;24:125.
681. Theiler A. J Comp Pathol Ther 1902;17:47.
682. Thiel PH van. Acta Leidensia 1960;30:123.
683. Toda T, Hiroki H. Ztschr Immunfschg Exp Ther 1934;82:1.
684. Todd JL. Proc Soc Exp Biol 1913;10:134.
685. Todd JL. Bull Soc Pathol Exot 1919;12:1290.
686. Tongeren HAE van, Koetsier JC. Ned Tijdschr Geneeskd 1968;112:1778.
687. Toyoda H. Kitsato Arch Exp Med 1919;3:42.
688. Toyoda H. Kitasato Arch Exp Med 1920;4:40.
689. Trautmann R. Ann Inst Pasteur 1907;21:808.
690.Trimarchi M. Boll Soc Ital Med Ig Trop Sez Eritrea 1942;1:93.
691. Troitskii NV. Med Parazitol 1945;14:70.
692. Tunnicliff R. J Infect Dis 1906;3:148.
693. Turner LH. Trans R Soc Trop Med Hyg 1968;62:880.
694. Uohara GI. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1967;24:113.
695. Uohara GI, Knapp MJ. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1967;24:113.
696. Vago S. Wien Med Wochenschr 1947;97:429.
697. Vaisman A, Hamelin A. Ann Inst Pasteur 1954;86:107.
698. Varma KC, Malik BS. Curr Sci 1968;37:170.
699. Varma MGR. Ann Trop Med Parasitol 1956a;50:1.
700. Varma MGR. Ann Trop Med Parasitol 1956b;50:18.
701. Varma MGR. Trans R Soc Trop Med Hyg 1956c;50:234.

702. Vassiliadis P, Jardin J. Ann Soc Belg Med Trop 1930;10:133.
703. Veld RG van der. Ned Tijdschr Tandheelk 1967;74:628.
704. Vertogradova TP. Antibiotiki 1957;3:44.
705. Vigors FGK. Rev Ecuator Hig Med Trop 1944;1:362.
706. Vincent H. Ann Inst Pasteur 1896;10:488.
707. Vincent R. Ann Inst Pasteur 1927;41:131.
708. Wagner–Jevseenko O. Acta Trop 1958;15:118.
709. Walters JH. In: Woodruff AW, Walters JH. Recent Advances in Tropical Medicine, 3rd ed. London: J & H Churchill Ltd.; 1961.
710. Walton GA. East Afr Med J 1951;28:189.
711. Walton GA. Trans R Soc Trop Med Hyg 1953;47:410.
712. Walton GA. East Afr Med J 1955;32:377.
713. Walton GA. Bull Entomol Res 1957;48:669.
714. Walton GA. Proc R Soc London Entomol 1959;34:63.
715. Walton GA. Symp R Zoolog Soc London 1962;6:83.
716. Wang CW, Lee CU. Chinese Med J 1936;50:241.
717. Wanhill AJ. J R Army Med Corps 1919;33:178.
718. Ward AR, Gallagher BA. Diseases of Domestic Birds. New York, NY: Macmillan Co.; 1920.
719. Weichbrodt R. Ztschr Immunfschg 1921;33:267.
720. Weiss E. J Lab Clin Med 1929;14:1191.
721. Weitz B, Buxton PA. Bull Entomol Res 1953;44:445.
722. Weller B, Graham GM. JAMA 1930;95:1834.
723. Westphal A. Arch Hyg Bacteriol 1963;147:349.
724. Weyer F. Ann Rev Entomol 1960;5:405
725. Weyer F. Ztschr Tropenmed Parasitol 1968;19:344.
726. Weyer F, Mooser H. Ztschr Tropenmed Parasitol 1957;8:294.
727. Wheeler CM. Am J Trop Med 1938;18:641.
728. Wheeler CM. Am Assoc Adv Sci Symposium No. 18, 1942;89.
729. Wheeler CM. J Parasitol 1943;29:33.
730. Wheeler CM, Herms WB, Meyer KF. Proc Soc Exp Biol Med 1935;32:1290.
731. Whitmore ER. In: Tice F. Practice of Medicine. Hagerstown, MD: WF Prior Co.; 1930.
732. Whitmore ER. In: Tice–Harve. Practice of Medicine, 4th ed. Hagerstown, MD: WF Prior Co.; 1966.
733.Wilcox C. Trop Med Bull 1944;41:791.
734. Willcox WH. Proc R Soc Med 1920;13:59.
735. Wilson GS, Miles AA. Principles of Bacteriology and Immunity, 5th ed. Baltimore, MD: Williams & Wilkins Co.; 1964.
736. Wolman B, Wolman M. Ann Trop Med Parasitol 1945;39:82.
737. Wolstenhome B, Gear JHS. Trans R Soc Trop Med Hyg 1948;41:513.
738. Wood RC, Dixon KC. Br Med J 1945;ii:526.
739. Wright HD, Harold CHH. J R Army Med Corps 1919;35:203.
740. Wynns HL. Am Assoc Adv Sci Symposium No. 18, 1942;100.
741. Wynns HL, Beck MD. Am J Public Health 1935;25:270.
742. Yeo RM. South Afr Med J 1950;24:457.
743. Young H. Ann Biol Clin 1951;9:318.
744. Zaharia NI. Rev Stiint Med Bucurest 1948;57:209.
745. Zarafonetis CJD, Ingham HS, Berry JF. J Immunol 1946;52:189.
746. Zhordania–Rapava TK. Med Parazitol 1958;27:397.
747. Zuelzer M. J Trop Med 1936;39:204.
748. Zumpt F. Nature 1959;184:793.
749. Zumpt F, Organ D. South Afr J Lab Clin Med 1961;7:31.

INFORMATION FOR CONTRIBUTORS

Journal of Spirochetal and Tick-borne Diseases

Dedicated to science and art in spirochetal and tick-borne diseases

INFORMATION FOR AUTHORS AND EDITORIAL POLICY

The following guidelines are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" and the International Committee of Medical Journal Editors (the "Vancouver Group") statement, agreed at the January 1993 Meeting.

The *Journal of Spirochetal and Tick-borne Diseases* publishes quarterly reviews and original work studies about any aspect of spirochetal and tick-borne diseases. The primary purpose is to broaden our understanding of spirochetal and tick-borne diseases. Special focus is given to Lyme borreliosis (also known as Lyme disease), as the most prevalent spirochetal and tick-borne disease. The clinical topics may involve all medical disciplines, nursing, and pharmacy, as well as the social, ethical, and biological features of spirochetal and tick-borne diseases.

Reviews

Each issue includes a series of state-of-the-art articles on a topic related to spirochetal and tick-borne diseases. The articles represent invited presentation by authorities in the field on topics related to spirochetal and tick-borne diseases, with an emphasis on Lyme borreliosis.

Submissions to this category should present a comprehensive state-of-the-art analysis and should be accompanied by an abstract of 300 words or less summarizing major points.

Peer Review Articles

Original articles of 5000 words or less may be submitted to the editorial office. Each article should be accompanied by an abstract of 300 words or less describing the findings of the original research. All articles will be peer reviewed within a 3-week period with subsequent notification to the authors within 5 weeks of submission.

Case Reports

Specific clinical case reports describing a unique approach to Lyme disease and other related disorders in the area of diagnosis or treatment may be submitted for review. An abstract of 250 words or less should accompany the text.

Photographic Section

The topical photographic section will be a regular feature. Photographs pertinent to articles presented in the Journal, as well as other photographs related to any aspect of spirochetal or tick-borne diseases, will be considered for the publication. The guidelines for the submission are designated in **Illustrations**.

Conflict of Interest

The Journal asks authors to disclose at the time of submission any financial or other arrangements they may have with a company whose product figures in the submitted manuscript or with a company making a competing product. Such information will be held in confidence while the paper is under review and will not influence the editorial decision, but if the article is accepted for publication, the editors will discuss with the authors the manner in which such information is to be communicated to the reader.

Submission of Manuscript

An original and three copies of the manuscript should be submitted to:

Journal of Spirochetal and
Tick-borne Diseases
SLACK Incorporated
6900 Grove Road
Thorofare, NJ 08086

Manuscripts containing original material are accepted with the understanding that neither the article nor any

part of its essential substance has been or will be published or submitted for publication elsewhere before appearing in the Journal.

All manuscripts should be accompanied by a letter of copyright transmittal. This must be signed and dated by all authors. The letter is required before any manuscript can be considered for publication and should contain the following wording:

"In consideration of The Lyme Disease Foundation taking action in editing my (our) submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to The Lyme Disease Foundation. The copyright so conveyed includes any and all subsidiary forms of publication, such as electronic media. The author(s) declares that the manuscript contains no matter that is, to the best of the author's knowledge, libelous or unlawful, or that infringes upon any U.S. copyright."

All manuscripts should be submitted with a cover letter indicating the category for which the manuscript should be reviewed. Copies of any closely related manuscripts should be submitted to the Editor along with the manuscript that is to be considered by the journal.

Titles and Author's Names

With the manuscript, provide a page giving the title of the article; titles should be concise and descriptive (not declarative). Also include a running head of fewer than 40 letter spaces; the name(s) of the author(s), including the first name(s) and academic degree(s); the name of the department and institution in which the work was done; the institutional affiliation of each author; and the name and address of the author to whom reprint requests should be addressed. Any grant support that requires acknowledgment should be mentioned on this page.

Abstract

Provide on a separate page an abstract of not more than 300 words (original and review articles) or 250 words (case report). This abstract should consist of four paragraphs, labeled Background, Methods, Results, and Conclusion. They should briefly describe the problem being addressed in the study, how the study was performed, the results, and what the authors conclude from the results.

Text

All material should be typed and double-spaced. Standard sequence of methods and materials, results, and discussion should be employed with tables and figures numbered in the order in which they are cited in the text. A disk in text format should accompany this.

Tables

Submit tables typed and double-spaced and provide a heading for all columns with a comprehensive title on separate sheets. A disk copy with a separate file for each table should be on the disk containing the text.

Illustrations

Photographs and figures should be submitted as glossy prints 5×7 in., with one copy of each print for each copy of the manuscript. Figure legends should be provided on a separate sheet with identification of the figure. The back of the glossy print should indicate the number of the figure.

References

References should be numbered in order of citation in the text, following the American Medical Association guidelines for references. The standard journal abbreviations from *Index Medicus* should be followed. Numbered references to personal communications, unpublished data, and manuscripts either "in preparation" or "submitted for publication" are unacceptable.

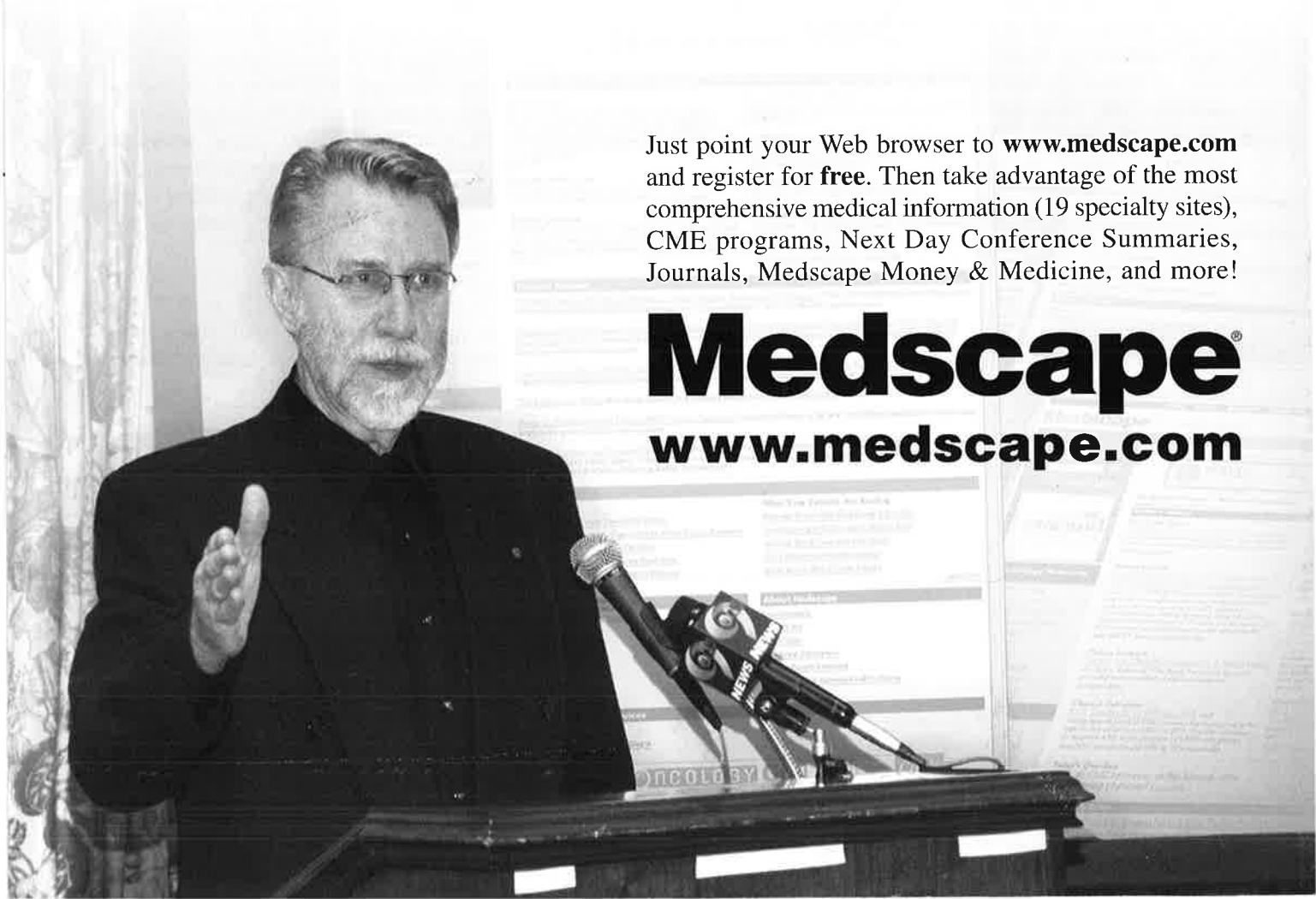
Drug Names

Generic names generally should be used. When proprietary brands are used in research, include the brand name in parentheses in the Methods section.

Why George D. Lundberg, MD, Chose to Join Medscape as Editor in Chief

The Web is revolutionizing access to healthcare information, and Medscape has set the standard of excellence in the medium. I am joining a team that is as passionate and dedicated as I am about improving healthcare by providing the highest-quality information possible. Medscape's authoritative Web site and its talented team of editors and executives were critical factors in my decision.

— George D. Lundberg, MD
formerly Editor of *JAMA* for 17 years;
Medscape member since 1996



Just point your Web browser to **www.medscape.com** and register for **free**. Then take advantage of the most comprehensive medical information (19 specialty sites), CME programs, Next Day Conference Summaries, Journals, Medscape Money & Medicine, and more!

Medscape®

www.medscape.com