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 2,860 cases in 1950. The number of annually reported instances increased to 7,499 in 1953 and 8,760 in 1959, with a low of 2,760 in 1961. The number increased to 5,971 in 1964 and came to 3,729 in 1968. All provinces are infected at present (1969-1970) and the number of reported cases has not been below 2,760 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 1,948 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. Fig. 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-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 1880's 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 1,000 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 Eastasian 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 tick-borne 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 bor-

reliae 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 semi-desert 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 (U.S. 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 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

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

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 cold-blooded 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

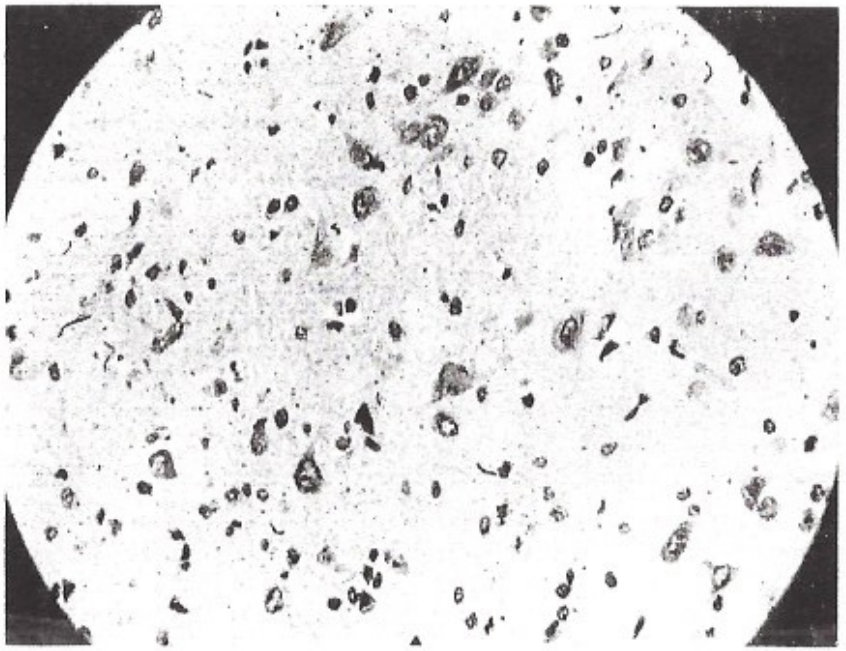

FIGURE 29. Gliosis and neuron cell damage in relapsing fever.

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 (R.E.S.) 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 (C.N.S.) 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 Martínez 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 R.E.S. 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

*Our recent experiments in patas monkeys (Exptl. Molec. Path., *12:255*, 1970) demonstrated the role of tRNA-ribosomal participation in this process.

lyse borreliae, after which phagocytosis may take place, with R.E.S. 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 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 R.E.S. 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 S.G.O.T. and S.G.P.T. 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

Continued in Next section.